An Exploration of the Mental Health Experiences of Young Women with Diminished Ovarian Reserve

Brittany M. Woods

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AN EXPLORATION OF THE MENTAL HEALTH EXPERIENCES OF YOUNG WOMEN WITH DIMINISHED OVARIAN RESERVE

by

BRITTANY M. WOODS

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A DISSERTATION
Submitted to the graduate faculty of The University of Alabama at Birmingham, in partial fulfillment of the requirements for the degree of Doctor of Philosophy

BIRMINGHAM, ALABAMA
2023
AN EXPLORATION OF THE MENTAL HEALTH EXPERIENCES OF YOUNG WOMEN WITH DIMINISHED OVARIAN RESERVE

BRITTANY M. WOODS

NURSING

ABSTRACT

Infertility is a reproductive disease resulting in the inability to conceive. One in six individuals will experience infertility in their lifetime. Diminished ovarian reserve (DOR) reduces the quantity and/or quality of a female's oocyte pool and is a known cause of infertility. Although this occurs during normal ovarian aging in the late 30s and early 40s, DOR can also impact younger women, increasing their risk for psychological distress from an unexpected diagnosis. The purpose of this dissertation is to develop a deeper understanding of the mental health experiences of young women with DOR through the generation of three manuscripts. Manuscript one examined the concept of infertility-related stress. Attributes included loss of identity, relational strain, isolation, stigma, anxiety, depression, and reduced self-esteem. Consequences included decreased quality of life, premature discontinuation of treatment, relational strain, anxiety, depression, and reduced self-esteem. Manuscript two reviewed strengths and limitations of the Fertility Quality of Life (FertiQoL) tool and described its psychometric properties and utility in research and clinical practice. Findings indicated the FertiQoL is a sound measurement with satisfactory face, content, convergent, and structural validity, and adequate internal consistency. Manuscript three investigated the mental health experiences of young women with DOR through a phenomenological approach. Participants described several reactions to DOR, including shock, loneliness, anxiety, and depression. Two main themes emerged: 1) Young women with DOR feel like a
“forgotten community” coping with an invisible disease; and 2) Not all fertility clinics are created equal. Participants perceived the DOR diagnosis as devastating and hopeless, urging others to find providers with DOR expertise. This study established how young women with DOR perceive their mental health and identified a significant need for holistic and goal-concordant infertility health care. Women with DOR should be educated about their diagnosis, afforded transparent and realistic treatment expectations, offered mental health resources, and counseled about potential psychological consequences during and beyond their infertility journey.

Keywords: infertility, mental health, fertility quality of life, diminished ovarian reserve, phenomenology
DEDICATION

To

Chad, Mom, Kay, and Ricky

This dissertation is dedicated to all those struggling with infertility, those who refuse to be silent, and those without the words and voice to speak. I see you. I hear you.

IN MEMORY OF

Dad
You will always be loved and never forgotten. Thank you for passing on to me an endless love of travel, an appreciation for fine things (you’re welcome, Chad), an eternal spirit of curiosity and mischievousness, and most importantly, not enough sense to know when to give up. I love and miss you.
ACKNOWLEDGMENTS

Chad,
My love, my life, my support, & my home. Thank you for your immeasurable love, never-ending reassurance, and our lifetime of adventures. No matter where our journey takes us, I will always be home as long as I'm with you.

Mom, thank you for your unending love, support, and encouragement. You truly are my best friend and my north star. Here’s to many more years of solving the world’s problems together. I love you.

Kay and Ricky, thank you for always looking out for us, for making dinner when I was just too tired, and always being a place I could find comfort, food, and humor.

Dr. Sigrid Ladores and my dissertation committee, thank you for all of your support and encouragement. Without your guidance, this dream would have never been achieved.

Coffee and whiskey – you know what you did…
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<th>Description</th>
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<td>ART</td>
<td>Assisted reproductive technology</td>
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<td>DOR</td>
<td>Diminished ovarian reserve</td>
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<td>FertiQoL</td>
<td>Fertility quality of life</td>
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<td>FPI</td>
<td>Fertility Problem Inventory</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<td>ICSI</td>
<td>Intracytoplasmic sperm injection</td>
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<td>IUI</td>
<td>Intra-uterine insemination</td>
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<td>IVF</td>
<td><em>In-vitro</em> fertilization</td>
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<td>Principal Investigator</td>
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<td>PSS</td>
<td>Perceived Stress Scale</td>
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<td>QR</td>
<td>Quick Response</td>
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<td>STAI</td>
<td>State-Trait Anxiety Inventory</td>
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CHAPTER 1

INTRODUCTION

Infertility is a disease of the reproductive system that renders an individual unable to conceive after 12 months of unprotected sexual intercourse (Practice Committee of the American Society for Reproductive Medicine, 2013; World Health Organization, 2022). It affects millions of individuals and couples worldwide (Boivin et al., 2007; Mascarenhas et al., 2012) and is caused by various factors and underlying etiologies, such as poor sperm quality or quantity, endometriosis, polycystic ovarian syndrome, and diminished ovarian reserve (DOR; Pastore et al., 2017; Penzias et al., 2021). DOR indicates a reduction in the quantity and/or quality of a female's oocyte pool available for fertilization based on current age (Penzias et al., 2021). While DOR typically affects women experiencing normal ovarian aging around the mid to upper 30s and 40s, it can also impact those who are younger (Practice Committee of the American Society for Reproductive Medicine, 2015).

Individuals and couples diagnosed with infertility can experience detrimental impacts to their physical, psychosocial, and financial health due to their disease process (Greil et al., 2011; Rostad et al., 2014; Woods et al., 2022). In addition, women who experience an early onset of DOR before age 35 may be at an increased risk for mental health challenges because of the unexpected diagnosis (Nikolaou & Templeton, 2004; Rasool & Shah, 2017). While some evidence suggests that women with DOR experience
poorer psychological health than those with other etiologies, such as anatomical causes (Nicoloro-SantaBarbara et al., 2017), no known studies have specifically explored the mental health experiences of young women diagnosed with DOR.

This dissertation will be accomplished by generating three manuscripts that build on each other and culminate in a better understanding of the mental health experience of young women with DOR. The purpose of this chapter is to 1) introduce the research problem; 2) provide the background and significance of the problem; 3) describe the purpose of this dissertation study and the three manuscripts; 4) outline the research questions; and 5) define key terms used in this dissertation. The first manuscript will present a concept analysis that will define infertility-related stress and its impact on those with infertility. The second manuscript will analyze a gold-standard measurement for fertility quality of life and describe both its strengths and weaknesses in understanding infertility's impact on mental health. The third manuscript will discuss the findings from a phenomenological study examining the lived experiences of mental health of young women with DOR. The final chapter will include research implications from the three manuscripts, discuss potential implications for patient care, and suggest areas of future research for women with DOR.

**Problem Statement**

Although a reduction in the oocyte pool at any age can cause infertility and is considered DOR (Practice Committee of the American Society for Reproductive Medicine, 2015), an early onset of DOR before age 35 may be unexpected, potentially
altering young women’s experiences of mental health during infertility (Nikolaou & Templeton, 2004; Rasool & Shah, 2017).

**Background and Significance**

One in six individuals will experience infertility in their lifetime (Geneva: World Health Organization, 2023) with six million women of childbearing age impacted in the United States (U.S.) alone (Center for Disease Control and Prevention, 2019). It can be categorized as “primary” if no previous pregnancies have been achieved, or “secondary” for those with at least one successful prior pregnancy and live birth (Zegers-Hochschild et al., 2017). Infertility can be female-specific, male-specific, or a combination of female and male factors and include etiologies such as abnormal sperm quantity or morphology, uterine abnormalities, ovulatory dysfunction, endocrine disorders, or DOR (Penzias et al., 2021).

Ovarian reserve testing is often an integral part of diagnosing infertility as it assesses the quantity of a woman’s remaining oocyte pool and reflects a female’s reproductive potential (Gleicher et al., 2011). A decline in ovarian reserve and reproductive potential usually begins in the mid-30s, but it can also affect women in their 20s and early 30s (Pastore et al., 2017). Women with DOR typically experience regular menstrual cycles but do not usually present with any outward symptoms other than the inability to conceive (Nikolaou & Templeton, 2004; Rasool & Shah, 2017). Because of a lack of consensus regarding the most appropriate and accurate diagnostic test to determine ovarian reserve, many patients are diagnosed with DOR by a specialist or reproductive endocrinologist when they seek answers to their reason for infertility, and
frequently in conjunction with treatments, such as assisted reproductive technology (ART; The Practice Committee of the American Society for Reproductive Medicine, 2012; Tremellen & Savulescu, 2014). In 2019, 298,689 cycles of ART were reported to the Society for Assisted Reproductive Technologies (Society for Assisted Reproductive Technology, 2019). Of these cycles, 39,450 (13%) were diagnosed with DOR, and 3,264 (8% with DOR; 1% of the total cycles) were 40 years of age or younger.

Involuntary childlessness and determining a path to parenthood can create significant emotional turmoil (Galst, 2018), with women with infertility reporting experiencing anxiety and/or depression symptoms 25-60% of the time, similar to those with other chronic health conditions (Domar et al., 1992; Rooney & Domar, 2018). While it is well established that infertility causes psychological stress, high rates of anxiety and depression among those with infertility suggest that significant gaps still exist in addressing the mental health care needs of patients with infertility (Aarts et al., 2012; Cousineau & Domar, 2007; Gameiro et al., 2013). Infertility-related stress can have a detrimental impact on patients’ physical, mental, and financial health and quality of life and ultimately contribute to poor psychological outcomes if left unaddressed (Rostad et al., 2014). Consequently, patients desire additional mental health support and education as many perceive a lack of emotional support and mental health screenings from their reproductive health providers (Gelgoot et al., 2020; Hoff et al., 2018; Salakos et al., 2004). In addition, with limited insurance coverage options for infertility treatments, patients with infertility face substantial out-of-pocket costs, potentially limiting reproductive options for those unable to afford care and further compounding infertility-

Although a reduction in the oocyte pool at any age is considered DOR (Practice Committee of the American Society for Reproductive Medicine, 2015), younger women may have different mental health experiences stemming from the increased psychological burden of an unexpected diagnosis (Nikolaou & Templeton, 2004; Rasool & Shah, 2017). Furthermore, evidence suggests that women with DOR suffer from poorer psychological health than those with other etiologies of infertility, like anatomical causes (Nicoloro-SantaBarbara et al., 2017). Women diagnosed with DOR at an early age are also at a higher risk for experiencing long-term physical effects extending beyond reproduction and immediate quality of life, such as premature ovarian insufficiency, decreased bone mineral density, sexual distress, and disturbed sleep patterns (Pal et al., 2010). However, because of the limited evidence of the mental and physical consequences of DOR, there is a dearth of understanding of how young women with DOR perceive their mental health and mental health care during infertility.

**Purpose Statement**

The purpose of this dissertation is to develop a deeper understanding of the mental health experience of young women with DOR by examining the concept and consequences of infertility-related stress (manuscript one), the strengths and limitations of the Fertility Quality of Life tool (FertiQoL; Boivin et al., 2011) (manuscript two), and the mental health of young women with DOR (manuscript three). The purpose of manuscript three will be achieved using a phenomenological exploration of the lived
experiences of infertility and mental health in women who have been diagnosed by age 35 with infertility caused by DOR in the United States. For this study, the mental health experience of young women with DOR will be generally defined to include experiences of depression, anxiety, infertility-related stress, and perceived met or unmet needs of infertility-related mental health care in women who have been diagnosed with DOR by their health care provider by age 35.

Overview of the Three Manuscripts

Manuscript 1 – Infertility-Related Stress: A Concept Analysis

The first manuscript aims to provide a clear definition of infertility-related stress and situate it within the mental health experience of infertility. This manuscript reviews all relevant and available literature based in the U.S. and outlines the antecedents, attributes, consequences, and role of infertility-related stress in the lives of individuals with infertility and their health care providers. This concept analysis also reviews how to identify and quantify infertility-related stress so that patients who need specialized care can be readily identified and evaluated. One measurement that can assist providers in identifying patients experiencing increased levels of infertility-related stress will be examined in manuscript two. The questions that guide the review include: 1) How is infertility-related stress defined for women with infertility? 2) What signs or symptoms do women with infertility-related stress present with? and 3) What are the consequences of infertility-related stress?
Manuscript 2 – Psychometric Properties and the Role of the Fertility Quality of Life Tool in Understanding Mental Health Consequences of Infertility

The purpose of manuscript two is to describe the development and evaluation of the FertiQoL tool, including an analysis of psychometric properties and implications for use in research. This manuscript examines all of the studies that have used the FertiQoL and reported psychometric properties since its inception. Results from this manuscript identify the limitations and challenges of using a quantitative measurement, including the inability to capture the nuances and essence of the lived experience that only a qualitative approach can accomplish.

Manuscript 3 – A Phenomenological Exploration of the Mental Health Experience for Young Women with Diminished Ovarian Reserve

The purpose of manuscript three is to describe the lived experiences of infertility and mental health in young women diagnosed with infertility caused by DOR in the United States. A phenomenological approach of inquiry is used to gain insight into the lived experiences of young women with DOR through the participant's own words. For this study, the mental health experience of young women with DOR is generally defined to include experiences of depression, anxiety, infertility-related stress, and perceived met or unmet needs of infertility-related mental health care in women who have been diagnosed with DOR by age 35 by their health care provider. Two research questions elicited the essence of the lived experiences of young women with DOR. 1) How do women diagnosed by age 35 with infertility caused by DOR describe their mental health during infertility? 2) How do women diagnosed by age 35 with infertility caused by DOR perceive their mental health care?
Overview of the Theoretical Framework

Theory of Stress and Coping

An adaptation of the theory of stress and coping was used as a theoretical model to guide the qualitative data collection and understand the perceived needs of patients with DOR, how they experience infertility and the psychological effects of their diagnosis and treatments. Lazarus and Folkman (1984) explain that the Theory of Stress and Coping focuses on psychological coping responses to stressful situations through appraisals based on a person-environment relationship (McEwen & Wills, 2019). This relationship includes moderators, like values, beliefs, support systems, and sociocultural factors that affect the appraisal of the stress event, generate emotion, and influence the coping process and outcomes (Folkman & Lazarus, 1988; Lazarus & Folkman, 1984). Conversely, coping is considered a mediator between the appraisal and emotional response that is either effective or ineffective and evaluated by examining psychological, social, and physical health and well-being (McEwen & Wills, 2019).

Adaptation of the Theory of Stress and Coping

Infertility can be a source of immense stress for those who desire parenthood and can result in long-term consequences of anxiety and depression (Rooney & Domar, 2018). The theory of stress and coping provides a theoretical base to examine the psychological aspects of the lived experiences of young women with DOR and helps explain how individuals present with different perceptions of their lived experiences of mental health and mental health care during infertility. An infertility-specific adaptation of the Theory
of stress and coping was made for this dissertation to help clarify relationships between the infertility-specific moderators and the adaptational outcomes.

The appraisal of the stress event, being diagnosed with DOR, and ultimately the psychological outcomes are moderated by factors specific to an individual’s values and beliefs, like the importance of parenthood, the cause of infertility, personal and social resources and support, duration of infertility, sociodemographic factors such as age and financial stability, and previous diagnoses of anxiety or depression (Drosdzol & Skrzypulec, 2009; Maroufizadeh et al., 2018; Omani-Samani et al., 20118). Additionally, Lazarus and Folkman’s original model described two main types of coping. However, additional adaptations were made to reflect findings from previous studies in which individuals with infertility utilized four main coping styles: active avoidance, passive avoidance, active confronting, and meaning-based coping (Martins et al., 2011; Schmidt et al., 2005).

Chapter 1 Summary

The overall purpose of this study is to provide a deeper understanding of the mental health experiences of young women with DOR and their perceptions of mental health care during infertility. The first manuscript provides a clear definition of infertility-related stress, including subsequent consequences in the lives of individuals with infertility. The second manuscript describes the psychometric properties and limitations of the FertiQoL tool, including the inability of quantitative measurements to capture the essence of the lived experience that only a qualitative approach can accomplish. The third manuscript provides valuable insight into the lived experiences of
mental health for young women with DOR through the participant's own words. Chapter one has introduced the problem, background and significance, purpose, an overview of the three manuscripts, and definitions of key terms. The last chapter of this dissertation will combine and synthesize the findings from the three manuscripts to provide a comprehensive understanding of how a diagnosis of DOR at a young age influences the overall health and psychological well-being of young women, discuss implications for clinical care, and propose next steps for future research.
Key Terms and Definitions

This section provides definitions of the key terms that will be used throughout this dissertation.

1. *Diminished ovarian reserve*: A reduction in the quantity and/or quality of a female's oocyte pool that is available for fertilization based on current age (American College of Obstetricians and Gynecologists’ Committee on Gynecologic Practice & American Society for Reproductive Medicine, 2019; Pastore et al., 2017; Penzias et al., 2021).

2. *Fertility quality of life*: A subjective rating of one's life and the influences of fertility problems on general health, emotions, relationships, self-perceptions, work-life, and future life plans (Cardiff University, n.d.).

3. *Infertility*: A disease of the reproductive system that renders an individual unable to conceive or carry a child to term after 12 months of unprotected sexual intercourse (Practice Committee of the American Society for Reproductive Medicine, 2013; World Health Organization, 2022).

4. *Infertility-related stress*: Mental, emotional, or physical stress stemming from the inability to conceive children and/or infertility treatments (Woods et al., 2022).

5. *Anxiety*: Constant and excessive worrying that impedes daily activities and causes restlessness, fatigue, difficulty concentrating, or difficulty sleeping (American Psychiatric Association, 2021).

References


CHAPTER 2
AN INTEGRATIVE REVIEW OF THE LITERATURE

The purpose of this dissertation is to generate three manuscripts that will expand on the current understanding of the mental health of young women with infertility by examining infertility-related stress (manuscript one), fertility quality of life (manuscript two), and the lived experiences of young women with DOR (manuscript three). This literature review aims to understand the state of the science of infertility and mental health and how infertility affects young women with DOR. The purpose of this chapter is to support the need for an inquiry into the lived experiences of young women with DOR by presenting: (a) the epidemiologic basis and concepts of interest; (b) the search strategy used to obtain literature; and (c) an analysis of the current literature.

Epidemiologic Basis and Concepts of Diminished Ovarian Reserve

A recent survey from the National Survey for Family Growth indicated that approximately six million women of childbearing age in the United States are affected by infertility (Center for Disease Control and Prevention, 2019a). In 2019, 298,689 cycles of assisted reproductive technology (ART) using intrauterine insemination (IUI), in-vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI) were reported to the Society for Assisted Reproductive Technologies (SART; 2019). Of these cycles, 39,450
(13%) were diagnosed with DOR, and 3,264 (8% with DOR; 1% of the total cycles) were age 40 or younger.

**Search Strategy**

A literature search identified primary studies focused on DOR in women. The search was completed on June 26th, 2022, using PubMed via the National Library of Medicine, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost, and PsycINFO through ProQuest. The initial search strategy aimed to capture studies focusing on both DOR and mental health included the following keywords and Boolean operators: “diminished ovarian reserve” AND “depression” OR “anxiety” OR “mental health” OR “psychological distress.” However, the search resulted in a limited number of articles: PubMed returned seven results, PsycINFO returned three, and six were found in CINAHL. The choice was made to expand the search strategy using only the term “diminished ovarian reserve” in all three databases. With application of the “Human,” “Female,” and “English” filters, 565 records were available from PubMed, 107 results were available in CINAHL, and eight were available in PsycINFO.

The literature search resulted in 696 articles and results were imported into Covidence, a systematic review management system (www.covidence.org). After the removal of 123 duplicates, 573 records were available to screen. Criteria for inclusion included primary studies that: 1) include a population of females with DOR; 2) describe the measurement of DOR; 3) examine the risk factors or causes of DOR; and 4) examine the reproductive outcomes of patients with DOR. Meta-analyses, literature reviews, commentaries, case studies, and reports with less than five participants were excluded.
Following title and abstract screening, 434 records were excluded, leaving 139 records available for review. After screening full-text articles, 30 records were excluded. One could not be retrieved and was excluded for no full-text availability, five were excluded for focusing on the wrong patient population, five articles reported the wrong outcome measurements, six used the wrong study design, and 13 measured the wrong outcomes that were not of interest to the review. A final total of 109 articles were available for inclusion in the epidemiology review (See Figure 1 for PRISMA diagram).
**Figure 1**
*PRISMA for Diminished Ovarian Reserve and Mental Health Epidemiology*
Women with DOR often experience regular menstrual cycles and exhibit no outward symptomatology of infertility other than the inability to conceive, meaning they may not receive a diagnosis until they seek assistance for infertility from a reproductive specialist (Guzel et al., 2017; Nikolaou & Templeton, 2004; Rasool & Shah, 2017). Unfortunately, there is discord among professional societies and physicians about the diagnostic requirements and ovarian reserve parameters that indicate a DOR diagnosis, thus, one universally accepted definition of DOR remains elusive (American College of Obstetricians and Gynecologists’ Committee on Gynecologic Practice & American Society for Reproductive Medicine, 2019; Practice Committee of the American Society for Reproductive Medicine, 2015). Currently, no gold standard exists to adequately measure ovarian reserve, and the definition of DOR becomes muddled when clinicians and researchers interchange DOR with terms like poor ovarian response, premature ovarian failure, or ovarian insufficiency (Cohen et al., 2015; Pastore et al., 2017).

The European Society of Human Reproduction and Embryology (ESHRE) recommends meeting two out of three criteria in order to predict poor ovarian response (POR): 1) Maternal age of 40 or older or any condition/risk factor for POR; 2) Prior poor response (≤ 3 oocytes) with a previous ART cycle; and 3) Abnormal ovarian reserve test evidenced by antral follicle count <5-7 or anti-Müllerian hormone <0.5-1.1 ng/ml (Devine et al., 2015; Ferraretti et al., 2011). While DOR often leads to a poor response during ART, this definition would ultimately exclude young women who have yet to undergo an ART cycle, precipitating a higher degree of difficulty in accurately identifying young women with DOR (Devine et al., 2015). Several tests are available to
measure ovarian reserve and diagnose DOR, the most common being anti-Müllerian hormone, antral follicle counts, and follicle-stimulating hormones (American College of Obstetricians and Gynecologists’ Committee on Gynecologic Practice & American Society for Reproductive Medicine, 2019; Practice Committee of the American Society for Reproductive Medicine, 2015).

Follicle-Stimulating Hormone

Follicle-stimulating hormone (FSH) is a serum marker for ovarian reserve that increases with advancing age, with elevated levels typically indicating poor ovarian response to ART and decreased pregnancy rates (Practice Committee of the American Society for Reproductive Medicine, 2015). Women with DOR typically present with higher than normal age specific FSH values (Buyuk et al., 2011; Navot et al., 1987; Pal et al., 2010; Pal et al., 2008). Although FSH increases steadily with age, and an abnormally high FSH will almost always indicate DOR, many women diagnosed with DOR will not initially present with an abnormal FSH (Practice Committee of the American Society for Reproductive Medicine, 2015). However, this discordance minimizes with increasing maternal age, with normal FSH values more accurately predicting good ovarian response and elevated FSH values suggesting latent stages of DOR and a higher risk for poor ovarian response (N. Gleicher et al., 2010b).

Recent studies have suggested contradictory findings regarding FSH levels and live birth rates. One study found that in women less than 35 years of age, there was no correlation between elevated FSH levels and an increased risk of pregnancy loss (Bishop et al., 2017). Alternatively, others found that unexplained recurrent pregnancy loss was
significantly associated with increased FSH levels, regardless of age (Bishop et al., 2017; Gürbüz et al., 2004). In women over 35 years old, an increase in FSH may also be associated with a reduction in live birth rates (Bishop et al., 2017). These findings suggest a high prevalence of DOR in women with increased levels of FSH over the age of 35 and in women with unexplained recurrent pregnancy loss.

**Antral Follicle Count**

Antral follicle count (AFC) is an ultrasonographic measurement that uses the number of total antral follicles in both ovaries to predict ovarian reserve and response to ART (Practice Committee of the American Society for Reproductive Medicine, 2015). AFC steadily declines with age, with a significant decrease after age 35 (Bozdag et al., 2016). Similar to the contradictory findings of FSH, some studies suggest that a lower AFC, indicative of DOR, is predictive of pregnancy loss (Elter et al., 2005), while others found no association with pregnancy loss or live birth rates (Bishop et al., 2017). Regardless of the utility in predicting pregnancy loss and live birth rates, AFC is relatively useful for predicting ovarian response, with follicle counts before ovulation induction directly related to the number of retrieved oocytes (Loverro et al., 2003). Unfortunately, AFC measurements are highly reliant on human subjectivity, expertise, and ultrasound equipment that may vary in quality from clinic to clinic (Loverro et al., 2003; Practice Committee of the American Society for Reproductive Medicine, 2015) and may be subject to poor interrater reliability without adequate training and equipment.
**Anti-Müllerian Hormone: Quality Versus Quantity**

Compared to AFC and FSH, the anti-Müllerian hormone (AMH) has emerged as a novel serum marker of ovarian reserve that reflects the quantity of ovarian reserve indicated by ovarian response parameters in women with infertility. Patients identified as having normal ovarian reserve have better ART outcomes than those with lower ovarian reserve (Celik et al., 2012; Nakhuda et al., 2007; van Rooij et al., 2002). Alternatively, individuals with a low AMH indicative of DOR typically have fewer oocytes retrieved overall (Barad et al., 2011; Buyuk et al., 2011; Celik et al., 2012; Gnoth et al., 2008; Nakhuda et al., 2007; Tal et al., 2021; van Rooij et al., 2002) and more cycle cancellations due to an inadequate number of oocytes to justify a retrieval procedure (Buyuk et al., 2011; Celik et al., 2012; Nakhuda et al., 2007). Additionally, there are discrepancies regarding intracycle variability of AMH and determining what cut-off point offers the most accurate prediction of ovarian reserve. Some suggest that AMH has little to no intracycle variability and can be measured at any point (Buyuk et al., 2011; Celik et al., 2012; van Rooij et al., 2002), while others recommend measuring AMH only during the follicular phase to obtain the highest measurement (Gorkem et al., 2017). These discrepancies create potential challenges when interpreting AMH as the sole ovarian reserve marker.

While several studies suggest that AMH provides an adequate quantitative evaluation of ovarian reserve, the question remains as to whether or not it reflects oocyte quality. Aneuploidy (chromosomal abnormalities of the oocyte or embryo), clinical pregnancy rates, miscarriage rates, and live birth rates may be reflective of oocyte quality. Positive correlations have been found between AMH levels, clinical pregnancy
(Gnoth et al., 2008; Reijnders et al., 2016), and live birth rates (Norbert Gleicher et al., 2010; Reijnders et al., 2016; Tal et al., 2021). In addition, a link may exist between low AMH levels and increased miscarriage risks (Lyttle Schumacher et al., 2018). This may be partly due to an increase in aneuploidy with decreased AMH levels and increased maternal age (Jiang et al., 2018). Though ART consistently results in lower oocyte yields for patients with low AMH levels, the association between AMH and clinical pregnancy or live birth rates is not as clear (Pereira et al., 2016). One proposed explanation is that regardless of the AMH level or oocyte yield, once patients have viable embryos for transfer, they will experience acceptable pregnancy and live birth rates similar to those without DOR (Pereira et al., 2016). However, the key differentiating factor is the availability of a viable embryo, which not all patients exhibiting low levels of AMH will be able to achieve.

**Contributors, Causes, and Risk Factors**

**Predetermined and Nonmodifiable Risk Factors for DOR**

The literature identifies several risk factors and causes of DOR, including genetic mutations, cancers, sociodemographic and lifestyle factors, certain disease processes, and some medications. Improvements in genomics and chromosomal karyotyping have advanced our knowledge about chromosomal abnormalities and their potential link with infertility. A few of the mutations suspected to affect DOR include Trisomy X (Davis et al., 2020), FMR1, or the Fragile X gene (Gleicher, Weghofer, et al., 2009; Pastore et al., 2012), growth differentiation factor 9, or GDF9 (Wang et al., 2013), and FOXL2 mutations in patients with blepharophimosis-ptosis-epicanthus inversus syndrome (Meng...
et al., 2022). A younger age at menarche may also increase the risk for DOR (Sadrzadeh et al., 2003; Wang et al., 2013), but this is not always the case, with a mother’s age at menopause more predictive of DOR than the individual’s age at menarche (Moreau et al., 2018).

A high prevalence of DOR and primary ovarian insufficiency occur in childhood and adolescent cancer survivors, with patients exhibiting decreased AMH, AFC, and ovarian volume, as well as elevated FSH levels (Ayandari et al., 2022; Elchuri et al., 2016; George et al., 2019; Larsen, Müller, Rechnitzer, et al., 2003; Larsen, Müller, Schmiegelow, et al., 2003; Lunsford et al., 2014; Molinari et al., 2021; Parissone et al., 2021). Childhood and adolescent cancer survivors who have undergone gonadotoxic therapies, such as chemotherapy with alkylating agents and radiation, are also at a higher risk for DOR and primary ovarian insufficiency (Elchuri et al., 2016; George et al., 2019; Molinari et al., 2021). Young women with breast cancer, especially those with the BRCA1 mutation (Porcu et al., 2020), also present with low ovarian reserve markers indicative of DOR (Partridge et al., 2010). Based on these findings, it is evident that counseling for fertility preservation options should be a standard of care for all patients with cancer, especially those at high risk for developing DOR.

Several studies provide contradictory findings related to DOR in specific disease populations. While some indicate significant correlations between subclinical hypothyroidism (Michalakis et al., 2011; Rao et al., 2020) and thyroid autoimmunity with DOR (Hsieh & Ho, 2021), others found no significance (Ke et al., 2020; Polyzos et al., 2015), potentially owing this difference to the studied population of euthyroid women versus those with thyroid alterations and using different measures of ovarian reserve.
Other diseases have also been linked to DOR, with less contradictory results, including Fanconi anemia (Sklavos et al., 2014), Bechet’s disease (Mont'Alverne et al., 2015), and myotonic dystrophy (Srebnik et al., 2014), all evidenced by decreased AMH levels and/or increased FSH levels. An association may also exist between DOR and sickle cell anemia (Garba et al., 2021; Pecker et al., 2022), potentially due to the hydroxyurea treatments (Pecker et al., 2020; Pecker et al., 2022) and hematopoietic stem-cell transplants (Elchuri et al., 2020) often used as treatment for patients with sickle cell.

**Modifiable Risk Factors of DOR**

While certain risk factors, such as cancer, genetic mutations, disease processes, and age at menarche and menopause are nonmodifiable, some modifiable risk factors may directly impact ovarian reserve. Elevated body mass index (Buyuk, Seifer, Illions, et al., 2011), smoking (Sharara et al., 1994), and alcohol intake (Li et al., 2013; Wang et al., 2021) show associations with DOR. Additionally, previous studies have found associations between DOR and specific medications, such as thalidomide (Peng et al., 2017), oral cyclophosphamide in patients with Wegener’s (Clowse et al., 2011), and iron overload in patients with transfusion-dependent beta-thalassemia (Uysal et al., 2017). Adnexal surgeries, such as bilateral ovarian drilling (Kandil & Selim, 2005) and endometrioma cystectomies, have been found to lower ovarian reserve and diminish ART outcomes (Roustan et al., 2015; Wang et al., 2021). While these medications and surgical therapies may be necessary to treat the disease, patients should be counseled about the potential effects on ovarian reserve, and alternative options and fertility preservation should be offered when possible.
Assisted Reproductive Outcomes

Women with DOR are often termed poor responders to ART, as previously mentioned (Chang et al., 2018). Patients with DOR typically have fewer oocytes available for retrieval after ovarian stimulation (Buyuk, Seifer, Illions, et al., 2011; Chang et al., 2018; Kumbak et al., 2005; Tal et al., 2021), thus increasing the rates of cycle cancellation due to inadequate oocyte numbers (Buyuk, Seifer, Younger, et al., 2011; Kawwass et al., 2017) and increasing the chance for low or total fertilization failures (Tian et al., 2022). While one study found no association between DOR and a reduction in live birth rates (Bishop et al., 2017), substantial evidence suggests otherwise. Multiple studies have found evidence suggestive of both decreased clinical pregnancy (Hu et al., 2020; Magendzo et al., 2006; Navot et al., 1987; Scott et al., 1995) and live birth rates in women with DOR (Hu et al., 2020; Reijnders et al., 2016; Stern et al., 2013; Tal et al., 2021).

While achieving a clinical pregnancy is challenging for women with DOR, maintaining the pregnancy to achieve a live birth appears to be just as difficult. Women with DOR consistently demonstrate higher rates of pregnancy loss and miscarriage than women with normal ovarian reserve and other infertility etiologies (Levi et al., 2001; Lyttle Schumacher et al., 2018). Similar to other studies of women with DOR, several contradictory findings exist regarding pregnancy loss and DOR. In one study of approximately 1000 patients with elevated FSH levels, only 28 conceived and 20 of the patients (70%) experienced a reproductive loss (Levi et al., 2001). Others found only minor significance among women ages 30-34 (Hipp et al., 2016) or over the age of 35 (Bishop et al., 2017). A link has also been proposed between recurrent pregnancy loss
and DOR, suggesting that many women who present with unexplained recurrent pregnancy loss may have undiagnosed DOR evidenced by poor ovarian reserve markers (Atasever et al., 2016; Gürbüz et al., 2004; Trout & Seifer, 2000; Wald et al., 2020).

One explanation for lower pregnancy and birth rates and increased pregnancy loss in women with DOR is the presence of chromosomal aberrations (Zhang et al., 2021) and aneuploidy (N. Gleicher et al., 2010a; Gleicher, Weghofer, et al., 2009; Jaswa et al., 2021; Jiang et al., 2018; Katz-Jaffe et al., 2013), suggesting that, rather than just a quantitative reduction in the oocyte pool, women with DOR may also suffer from a qualitative reduction. Further evidence supports this by indicating that women with DOR who can obtain good quality oocytes and embryos indicated by visual inspection or preimplantation genetic testing will inevitably achieve similar clinical pregnancy and live birth rates to those without DOR (Chang et al., 2018; Kawwass et al., 2017; Pereira et al., 2016).

Alternative Therapies

Several alternative therapies and medications have emerged in the hopes of improving poor ovarian markers and poor ovarian response to ART in women with DOR. Dehydroepiandrosterone, or DHEA, is among the most studied and controversial supplement. DHEA has been touted to improve both the quality and quantity of oocytes by increasing the number of retrieved oocytes (Barad & Gleicher, 2006; Chern et al., 2018; Poli et al., 2014; Tsui et al., 2015), reducing the number of cycle cancellations (Barad & Gleicher, 2006; Poli et al., 2014), and improving ovarian reserve markers (N. Gleicher et al., 2010a; Tsui et al., 2015). Improvements in quality have been inferred by
increased fertilization rates (Barad & Gleicher, 2006; Chern et al., 2018; Tsui et al., 2015), normal day-3 embryos (Barad & Gleicher, 2006; Chern et al., 2018; Tsui et al., 2015), clinical pregnancy rates (Chern et al., 2018), and live birth rates (Chern et al., 2018). Findings have also suggested that DHEA may reduce miscarriage rates by reducing aneuploidy (Gleicher, Ryan, et al., 2009; N. Gleicher et al., 2010a). However, one study found no differences in oocyte or fertilization rates when pre-treating ART patients with DHEA (Kara et al., 2014). Small sample sizes, methodological differences, and multiple supplementation times and doses of DHEA may have contributed to the discrepancies, and randomized control trials should further investigate the utility of DHEA in DOR and ART.

Previous studies have also examined the effects of electroacupuncture and vitamin D supplementation on ovarian reserve markers. While vitamin D supplementation does appear to improve AMH (Aramesh et al., 2021; Bacanakgil et al., 2022), AFC (Bacanakgil et al., 2022), and FSH (Bacanakgil et al., 2022), the value of these results is limited only to women with DOR and vitamin D deficiency based on studies thus far. An alternative form of therapy, electroacupuncture, has also shown some potential use for improving ovarian reserve in women with DOR. After receiving 12 weeks of electroacupuncture (44 sessions), FSH significantly declined, suggesting an improvement in ovarian reserve (Wang et al., 2016). Future studies should focus on determining the efficacy of alternative therapies that could improve outcomes for DOR and poor responders.
**Long-Term Outcomes**

Low AMH levels indicative of DOR have been linked to several risk markers for cardiovascular diseases, such as insulin resistance, dyslipidemia (Al Rashid et al., 2020), and C-reactive proteins (Verit et al., 2016; Verit et al., 2014). However, small sample sizes preclude confidence in the results without more extensive longitudinal replication studies. Women with DOR may exhibit disturbed sleep (Pal et al., 2008), sexual dissatisfaction or sexual concerns (Nicoloro-SantaBarbara et al., 2017; Pal et al., 2008), and increased fertility distress (Nicoloro-SantaBarbara et al., 2017), which may impact their quality of life. Additional findings suggest that women with DOR are at an increased risk for loss of skeletal mass with low bone mineral density and bone turnover (Pal et al., 2008). Clinicians should counsel women with DOR about long-term health consequences outside of a reduced reproductive potential.

**Summary**

To this day, professional societies have failed to clearly define DOR. Most clinicians equate DOR with poor ovarian response, especially within the context of ART. Despite the numerous options available to measure ovarian reserve, no option emerges as the most accurate and consistent for diagnosing DOR and predicting ovarian response. Consequently, a recent review found that out of 14 research articles that defined DOR, only two teams shared a similar definition and included FSH > 10 IU/I as a marker of DOR (Cohen et al., 2015). The remaining 12 studies used different measurements and cut points to define DOR. Significant discordance has been found between testing results from AMH and AFC (Alebic et al., 2018) and between AMH and FSH (N. Gleicher et
AMH and AFC appear to be accurate predictors of ovarian response, and while FSH appears to be the most frequently used, it exhibits more inter- and intra-cycle variability. Although AMH seems superior to AFC and FSH when analyzed by itself, the predictive shortcomings for clinical pregnancy and live birth rates and the uncertainty of intracycle variability and reliability cannot be ignored. It is also of note that clinical pregnancy is not necessarily predictive of live birth, as many women with DOR experience high rates of pregnancy loss. Therefore, until more accurate predictive measurements of ovarian reserve are found, assessing the results of a combination of measures in concert with patient age will likely provide the best picture of ovarian reserve and predictions of clinical pregnancy and live birth rates (Gnoth et al., 2008; Practice Committee of the American Society for Reproductive Medicine, 2015).

As seen in studies about risk factors, causes, and treatments for DOR, findings related to this population tend to be contradictory and unclear at times. Few studies have found clear and robust evidence supported by additional research. This produces difficulties in the diagnosis and treatment of women with DOR. Additional health complications also suggest that DOR may result in long-term physical and mental health consequences reaching far beyond reproductive outcomes of clinical pregnancy and live birth rates. All of the findings combined suggest that women with DOR are a challenging population to identify, counsel, and successfully treat. Consequently, clinicians and patients face contradictory and sometimes unknown situations, further increasing distress for both parties.
Infertility and Mental Health Literature Review

Search Strategy

A literature search was performed to identify primary studies looking at psychological consequences (anxiety and depression) of infertility and diminished ovarian reserve. The search was completed on July 1st, 2022, using PubMed via the National Library of Medicine, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCOhost, and PsycINFO through ProQuest. Due to technological and practice changes in reproductive medicine, the literature search was restricted to the last ten years to ensure only relevant literature was obtained. The search strategy for PubMed and CINAHL included the following keywords and Boolean operators: “infertility, female” OR “female infertility” OR “infertility” OR “diminished ovarian reserve” AND “depression” OR “anxiety” OR “mental health” OR “mental health care” AND “woman” OR “women” OR “female” AND “middle aged” OR “adult.” After application of the “Human,” “Female,” “English,” and “Adult 19-64” filters, 410 records were available from PubMed, and 241 results were available in CINAHL. The search strategy was similar in PsycINFO with minor variations to meet the needs of the database: “diminished ovarian reserve” OR “infertility” AND “depression” OR “anxiety” OR “mental health” OR “mental health care” AND “woman” OR “women” OR “female” AND “adult” OR “middle-age.” After application of the “Human,” “Female,” “English,” and “Adult” filters and excluding books, dissertations, and reviews, 112 records were available.

The literature search resulted in 680 articles imported into Covidence, a systematic review management system (www.covidence.org). After the removal of 160
Duplicates, 520 records were available to screen. Criteria for inclusion included primary studies with a population of infertile females, psychological consequences of infertility or mental health care interventions, and for quantitative studies, a measurement of anxiety, depression, or both. Meta-analyses, literature reviews, commentaries, case studies, and reports with less than five participants were excluded. Studies focusing on one specific gynecologic disease other than DOR, such as endometriosis or polycystic ovarian syndrome, were also excluded. Following title and abstract screening, 450 records were excluded, leaving 70 records available for review. Four reports could not be retrieved and were excluded for no full-text availability, and seven were excluded for reporting the wrong outcome measurements. A total of 59 articles were available for inclusion in the current literature review (See Figure 2 for PRISMA diagram).
Figure 2
PRISMA for Infertility and Mental Health Literature
Results

Depression

Depression is one of the dominant variables identified in quantitative literature examining the impact of infertility on mental health. It can cause emotional and physical problems including sadness, a loss of interest in activities, difficulty sleeping, fatigue, and difficulty concentrating (American Psychiatric Association, 2020). Total reported rates of depression in women with infertility, including all levels of severity, vary widely among studies, from 13.8% - 83%, with most rates between 40%–70% (Al-Asadi & Hussein, 2015; Alhassan et al., 2014; Crawford et al., 2017; Lakatos et al., 2017; Maroufizadeh, Navid, et al., 2019; Maroufizadeh, Omani-Samani, et al., 2019; Peng et al., 2021; Shin et al., 2021; Valoriani et al., 2016; Zurlo et al., 2017). There is slightly less variability when looking specifically at moderate to severe and chronic anxiety, with moderate symptoms reported in 20%–50% of women (Al-Asadi & Hussein, 2015; Alhassan et al., 2014), moderate to severe symptoms in 17%–44% of women (Lakatos et al., 2017; Shani et al., 2016), severe depression in 7.5%–8% of women (Al-Asadi & Hussein, 2015; Xu et al., 2017), and a chronic trajectory of depression noted in 19.3% of women with infertility (Li et al., 2021).

Instruments. Depression measurements are used to report prevalence rates of depression, compare depression rates between populations and ART outcomes, and determine the efficacy of psychological interventions in reducing depression symptomology in women with infertility. The Beck Depression Inventory (BDI) was the most utilized depression instrument and was reported by 19 of the studies included in the
literature review (Gameiro et al., 2016; Pinto-Gouveia et al., 2012; Reis et al., 2013; Terzioglu et al., 2016; Yoldemir et al., 2020), followed by the Patient Health Questionnaire (Cai-Feng Bai et al., 2019; Dawadi et al., 2018; Maroufizadeh, Omani-Samani, et al., 2019; Shani et al., 2016; Shin et al., 2021). The Hospital Anxiety and Depression Scale (Biringer et al., 2015; El Kissi et al., 2013; Massarotti et al., 2019; van Dongen et al., 2016), Edinburgh Depression Scale (Valoriani et al., 2016; Valoriani et al., 2014; Zurlo et al., 2017; Zurlo et al., 2020), and the Center for Epidemiologic Studies Depression scale (Aimagambetova et al., 2020; Pasch et al., 2012; Peng et al., 2021) were the next most used and were equally represented. Less frequently used instruments were also reported, with limited utilization, including the Self-Rating Depression Scale (Li et al., 2021; Xu et al., 2017), NIH PROMIS screening tool (Crawford et al., 2017), Montgomery Asberg Depression Rating Scale (Koszycki et al., 2012), Depression Anxiety Stress Scale (Mousavi et al., 2020; Musa et al., 2014), and the Edinburgh Postnatal Depression Scale (Salih Joelsson et al., 2017).

**Risk factors.** Several factors have been identified that place women with infertility at an increased risk of depression. Females unequivocally experience higher rates of depression than men. Therefore, female sex is one of the most commonly noted risk factors for experiencing depression (El Kissi et al., 2013; Iordachescu et al., 2021; Musa et al., 2014; Pinto-Gouveia et al., 2012; Reis et al., 2013; Terzioglu et al., 2016; Yoldemir et al., 2020; Zurlo et al., 2020; Zurlo et al., 2018). Age has also been the subject of debate, with some finding that younger patients under age 35 are at a higher risk (Xu et al., 2017), with contradicting evidence suggesting those over age 35 are more
at risk (Zurlo et al., 2018). Educational attainment also appears to play a role, with lower levels of education increasing the risk for depression (Alhassan et al., 2014; Salih Joelsson et al., 2017; Xu et al., 2017; Zurlo et al., 2020; Zurlo et al., 2018). Female and unexplained infertility factors (Massarotti et al., 2019; Zurlo et al., 2020; Zurlo et al., 2018), higher durations of treatments (Al-Asadi & Hussein, 2015; Lakatos et al., 2017; Reis et al., 2013; Yoldemir et al., 2020), and infertility duration over 12 months (Biringer et al., 2015), more than two years (Crawford et al., 2017; Li et al., 2021; Maroufizadeh, Navid, et al., 2019; Salih Joelsson et al., 2017), more than three years (Alhassan et al., 2014; Zurlo et al., 2018), and from four to six years (Xu et al., 2017) are associated with an increased risk for depression. Nulliparous women with primary infertility (Al-Asadi & Hussein, 2015; Alhassan et al., 2014; Crawford et al., 2017; Yoldemir et al., 2020), those whose ART treatments are unsuccessful (Gameiro et al., 2016; Lakatos et al., 2017; Maroufizadeh, Navid, et al., 2019; Pasch et al., 2012; Terzioglu et al., 2016; Zurlo et al., 2018), and those who consequently remain childless after 20–23 years (Vikström et al., 2015) experience a significantly higher risk for depressive symptoms. Individuals with a history of psychiatric and mood disorders either prior to or during infertility are more likely to develop or maintain psychological problems years after ART discontinuation (Salih Joelsson et al., 2017; Volgsten et al., 2019). In addition, women who remain childless and have higher levels of depression are also at an increased risk for suicide (Shani et al., 2016), further reiterating the need for early psychosocial support and monitoring patients on a long-term basis.
Anxiety

In addition to depression, anxiety often plays a major role among women with infertility. Anxiety can manifest as constant and excessive worrying that impedes daily activities and causes restlessness, fatigue, difficulty concentrating, or difficulty sleeping (American Psychiatric Association, 2021). Compared to depression, anxiety rates exhibit slightly less variability with clinically significant anxiety reported in 24%–57% of women with infertility (Gameiro et al., 2016; Salih Joelsson et al., 2017; Xu et al., 2017; Zurlo et al., 2020). Incidences of severe anxiety are much lower, ranging from 2.2%–11.2% (Bashtian et al., 2018; Xu et al., 2017) and moderate to severe from 9.4 – 45% (Bashtian et al., 2018; Li et al., 2021; Shani et al., 2016). Anxiety often occurs in tandem with depression, impacting approximately 21%–37.3% of women with infertility (Lakatos et al., 2017; Musa et al., 2014; Xu et al., 2017), further reiterating the need for early identification and regular follow up with patients who experience psychological distress.

Instruments. The State-Trait Anxiety Inventory (STAI) is commonly used to assess anxiety in women with infertility, with 20 of the studies included in the review reporting results using the STAI (Aimagambetova et al., 2020; Chan et al., 2012; Iordachescu et al., 2021; Pedro et al., 2017), followed by the Hospital Anxiety and Depression Scale (Biringer et al., 2015; El Kissi et al., 2013; Massarotti et al., 2019; Salih Joelsson et al., 2017; van Dongen et al., 2016). The Self-Rating Anxiety Scale (Li et al., 2021; Peng et al., 2021; Xu et al., 2017), General Anxiety Disorder instrument (C. F. Bai et al., 2019; Omani-Samani et al., 2018; Shani et al., 2016), and the Beck Anxiety
Inventory (Bashtian et al., 2018; Clifton et al., 2020; Terzioglu et al., 2016) were the next most used and equally represented. The Hamilton Depression Scale-Anxiety (Koszycki et al., 2012) and Depression Anxiety and Stress Scale (Mousavi et al., 2020; Musa et al., 2014) were also used to a lesser extent.

**Risk factors.** Similar to depression, women with infertility (El Kissi et al., 2013; Musa et al., 2014; Omani-Samani et al., 2018; Terzioglu et al., 2016; Zurlo et al., 2018) and lower educational levels (Omani-Samani et al., 2018; Xu et al., 2017; Zurlo et al., 2018) experience anxiety at higher rates than males and those with higher educational attainment. There is a clearer association between younger age and increased anxiety in women than the conflicting correlations found between depression and age (C. F. Bai et al., 2019; Salih Joelsson et al., 2017; Xu et al., 2017). A longer duration of unresolved infertility (Li et al., 2021; Omani-Samani et al., 2018; Salih Joelsson et al., 2017; Xu et al., 2017; Zurlo et al., 2018) originating from a female factor (Bashtian et al., 2018; Massarotti et al., 2019; Zurlo et al., 2020), and longer duration of infertility treatments (Bashtian et al., 2018; Zurlo et al., 2018) are also associated with increased anxiety. However, some evidence suggests that women with infertility experience higher rates of anxiety during the initial versus repeated ART cycles, potentially owing this difference to the anxiety of the unknown (Zurlo et al., 2018). Also of significance, nulliparous women experience significantly increased anxiety after ART treatment failures (Omani-Samani et al., 2018; Pasch et al., 2012).
Resilience

Overall, resilience may be considered a protective factor against adverse psychological consequences of infertility. Resilience is the ability to maintain flexibility and mentally, emotionally, and behaviorally adapt to adverse events and external/internal demands (American Psychological Association, n.d.). Additionally, Bonnano (2004) describes four adjustment trajectories to adverse events: resilience, recovery, delayed, and chronic. Resilient trajectories are characterized by short-term minor disturbances that stabilize over time. Individuals who experience recovery trajectories encounter moderate to severe psychological distress that gradually returns to normal. Delayed trajectories result in moderate levels of distress that gradually worsen. Finally, chronic trajectories are characterized by an overwhelming amount of psychological distress that prohibits an individual from normal functioning over a period of time after the event.

Risk factors. Several studies indicate that lower resilience is associated with higher rates of anxiety and depression, lower quality of life, and premature discontinuation of infertility treatment (Bhamani et al., 2020; Gameiro et al., 2016; Li et al., 2021; You Jung & Hye Young, 2017). In addition, younger individuals with low levels of education, relational dissatisfaction, and inadequate social support are more likely to exhibit lower resilience (Gameiro et al., 2016; Li et al., 2021), with females generally demonstrating lower resiliency than their male counterparts (Bhamani et al., 2020). Alternatively, individuals with higher resiliency are more likely to utilize active coping skills (Sexton et al., 2009), while women with infertility who utilize emotional coping are more likely to report anxiety and depression (Musa et al., 2014). Of
significance, individuals displaying chronic trajectories of depression are more likely to be younger, have lower education, have a shorter duration of infertility, lower resilience, higher infertility stress, and higher baseline anxiety and depression scores (Li et al., 2021), while those in the resilient category are more likely to have successful ART outcomes, marital satisfaction, and adequate social support (Gameiro et al., 2016).
INFERTILITY-RELATED STRESS: A CONCEPT ANALYSIS

by

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Format adapted for dissertation
ABSTRACT

Aim: To develop a clear definition of infertility-related stress using Rodgers’ method of concept analysis.

Background: Infertility affects approximately 13% of women in the United States. Though poorly defined in the literature, previous studies suggest infertility-related stressors contribute to psychological distress.

Design: Rodgers' method of concept analysis guided the review, including sample and setting, literature search, and data analysis.

Data Source: PubMed, CINAHL, and PsycINFO were searched for relevant literature.

Review Methods: Following abstract, title, and text screenings, 21 articles were included and reported using the PRISMA-S checklist. Texts were analyzed and results informed the proposed definition of infertility-related stress.

Results: Antecedents included infertility, desire for children, and fear of the unknown. Attributes were identity crisis, social isolation and stigma, sexual stress, and financial strain. Consequences included treatment dropout and marital strain. Anxiety, depression, and decreased quality of life were identified as both attributes and consequences.

Conclusions: Synthesized results informed a proposed definition of infertility-related stress. Improved understanding of infertility-related stress allows for measurement development and facilitates recognition of patients in need of additional support, while potentially reducing the impact on the health and well-being of infertile women.

Keywords: infertility; psychological stress; infertility-related stress; concept analysis;
Rodgers’ evolutionary method
INFERTILITY-RELATED STRESS: A CONCEPT ANALYSIS

Infertility often creates an enormous burden stemming from financial, physical, psychosocial, and inter-relational stress (Galst, 2018; Greil, 1997; Greil et al., 2010; Rooney & Domar, 2018). The concept of infertility-related stress needs further analysis to determine the criteria used to define it, provide accurate measurement for studies utilizing it, and determine the significance of impact for women with infertility. The purpose of this article is to discuss findings of a concept analysis and provide a clear definition of infertility-related stress.

Background

Infertility affects approximately 13% of childbearing-age women in the United States (Center for Disease Control and Prevention, 2019b). For women with reproductive difficulties, receiving a diagnosis of infertility, processing provided information, and deciding on which path to parenthood to pursue can inflict emotional distress (Galst, 2018). Mounting costs of reproductive treatments and complicated comorbidities may limit treatment options for patients, further compounding infertility stress (Schneider & Forthofer, 2005). As of 2021, only 19 states require insurance coverage for infertility services, many with restrictions and stipulations, and some only covering diagnostic testing, but not treatments (RESOLVE: The National Infertility Association, n.d.). The cost of infertility treatments, also labeled fertility treatments in some literature, can range
from $10 for unmonitored, medicated cycles, $300–$3,000 for the least invasive artificially assisted cycles with intrauterine insemination, and between $10,000 and $28,000 for the most invasive in-vitro fertilization cycles (IVF), with costs highly dependent on geographic location and patient needs (Advanced Fertility Center of Chicago, n.d.).

An estimated 25%–60% of women with infertility report symptoms of depression and anxiety (Rooney & Domar, 2018), with depression levels comparable to patients with chronic illnesses (Domar et al., 1992). These staggering numbers highlight how crucial it is for clinicians to understand and address mental health in patients with infertility. If left untreated or unrecognized, physical, financial, and psychosocial stressors of infertility and its treatments can have detrimental effects on patients' health and well-being (Rostad et al., 2014).

Infertility-related stress is defined by multiple attributes. These include stress derived from the stigma surrounding infertility, loss of identity as a woman and prospective parent, inter-relational strain, financial burden, and psychosocial impacts (de Boer et al., 2020; Galst, 2018; Gerrity, 2001; Greil, McQuillan, et al., 2011). To clarify and define infertility-related stress, a concept analysis was performed, with the goal of identifying gaps in the current knowledge base and determining use of this concept within research and clinic settings. Further defining the concept will advance research and practice by allowing for enhanced recognition of symptoms, facilitating timely treatment of patients, and potentially reducing the impact of infertility-related stress on patients' health and well-being.
**Aims**

The purpose of this concept analysis is to provide a clear definition of infertility-related stress through the identification of antecedents, attributes, and consequences found in the available literature. The questions that guided the review were: (1) How is infertility-related stress defined for women with infertility? (2) What signs or symptoms do women with infertility-related stress present with? and (3) What are the consequences of infertility-related stress?

**Methods**

*Rodgers’ Method*

Using Rodgers' evolutionary method (2000), a concept analysis was performed to clarify infertility-related stress. This method is beneficial for concepts that are context-dependent, dynamic, and require identification of antecedents, attributes, and consequences for further clarification before being utilized in research (McEwen & Wills, 2019; Rodgers & Knafl, 2000). Rodgers' method of concept analysis includes six principal steps that aid in collecting, analyzing, and interpreting data (Rodgers & Knafl, 2000). These steps include: (1) identifying the concept and surrogate terms; (2) selecting a setting, sample, inclusion, and exclusion criteria for data collection; (3) collecting data, including attributes, antecedents, and consequences; (4) analyzing data; (5) identifying an exemplar when appropriate; and (6) interpreting data to define or clarify a conceptual meaning or to identify potential implications for additional research (McEwen & Wills, 2019; Rodgers & Knafl, 2000).
Concept Identification and Surrogate Terms

Although the term infertility-related stress is used frequently throughout the literature, the concept itself appears to be poorly defined and unclear in meaning. This lack of definition and clarity prompted the first step of analysis for infertility-related stress. Rodgers (2000), explains that surrogate terminology may be encountered as alternate expressions used to describe the same concept of interest. Surrogate terms identified during the analysis included infertility distress (Greil, 1997; Johnson & Fledderjohann, 2012; Miles et al., 2009), infertility stress (Ridenour et al., 2009), and fertility-specific distress (Greil, McQuillan, et al., 2011; Greil, Shreffler, et al., 2011; Johnson & Fledderjohann, 2012).

Setting and Sample

Following the second step of Rodgers' method, an appropriate setting and sample for data collection was determined. Due to the psychological aspects of infertility-related stress (Cousineau & Domar, 2007; Miles et al., 2009), a multidisciplinary approach to a literature search was utilized. PubMed, CINAHL, and PsycINFO were identified as relevant databases to execute the literature search. The sample included all indexed literature resulting from the combination of selected key terms and applied filters, with no date restrictions.

Data Collection

Data collection was completed using a discovery approach as the third step of the concept analysis. A review of literature was performed using three databases: PubMed
via the National Library of Medicine, CINAHL through the EBSCOhost platform, and PsycINFO using ProQuest. The PubMed search strategy included the following keywords and Boolean operators: "infertility-related stress" OR "infertility, female" OR "female infertility" OR "female subfertility" OR "secondary fertility" OR "postpartum sterility" OR "female sterility" AND "stress, psychological" OR "psychological stress" OR "financial stress.” After application of English and MeSH filters, 184 results were returned. Search strategies were similar in CINAHL with keywords including: "infertility-related stress" OR "fertility preservation" OR "infertility" OR "female infertility" OR "female subfertility" OR "secondary fertility" OR "postpartum sterility" OR "female sterility" AND "stress, psychological" OR "psychological stress" OR "financial stress.” After applying English and Female filters, 131 results were returned. PsycINFO was also utilized in the literature search and keywords included: "female infertility" OR "female subfertility" OR "secondary fertility" OR "postpartum sterility" OR "female sterility" OR "infertility-related stress" AND "psychological stress" OR "financial stress" OR “stress.” After the application of the English filter, 54 articles were returned. Search strategies and keyword modifications were needed based on individual database requirements. An additional 31 articles were identified through hand-searching article reference lists using the ancestry approach.

A total of 400 records were imported into Covidence, a systematic review management system, (www.covidence.org), and the search was concluded February 26, 2021. After removing 95 duplicates, 305 records were available to screen. Due to diverging cultural perceptions and varying emphases surrounding infertility-related stress attributes, such as cultural-specific infertility-related stigma (Bos et al., 2005; Nahar,
2012), non-US-based population records were excluded from the current analysis. Studies focusing on cancer or gynecological diseases were also excluded to better mitigate compounding stress factors affecting patients diagnosed with comorbidities such as genetic aberrations, cancers requiring fertility preservation, premature ovarian failure, and endometriosis. Systematic reviews, meta-analyses, and records including less than five participants were also excluded. Following title and abstract screenings, 259 records were excluded, leaving 46 records available for full-text review. Twenty-five full-text articles were excluded for reasons including 12 “did not meet inclusion criteria,” 10 “no full text available,” and 3 “wrong patient population.” A total of 21 articles were left for extraction and inclusion in the concept analysis for infertility-related stress (see Figure 1). A combination of quantitative (11), qualitative (1), position statements (2), and review articles (7) were included in the analysis. To reduce reporting bias, the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension checklist was used (PRISMA-S, Rethlefsen et al., 2021).

Data Analysis

After reviewing data in the literature review, an analysis was completed during step four. During this process, antecedents, attributes, con-sequences, and references of infertility-related stress were compiled and synthesized for review. See Table 1 for data analysis results.
Figure 1
PRISMA for Infertility-Related Stress Concept Analysis
<table>
<thead>
<tr>
<th>Source</th>
<th>Type: RV, RS\textsuperscript{QUAL}, RS\textsuperscript{QUANT}, PS</th>
<th>Results from extracted conceptual properties: ST, AN, AT, CO</th>
</tr>
</thead>
</table>
| Boulet et al. (2017) | RS\textsuperscript{QUANT} | AN: Infertility  
CO: Decreased quality of life |
| Cousineau and Domar (2007) | RV | AN: Infertility, Fear of the unknown  
CO: Infertility treatment dropout, Depression, Anxiety, Reduced self-esteem |
| Galst (2018) | RV | AN: Infertility, Fear of the unknown  
CO: Increased anxiety, Depression, Decreased quality of life, Infertility treatment dropout, Reduced marital satisfaction |
| Gerrity (2001) | RV | AN: Infertility, Desire for parenthood  
CO: Depression, Decreased quality of life, Reduced marital satisfaction, Reduced self-esteem |
| Greil (1997) | RV | ST: Infertility distress  
AN: Infertility, Fear of the unknown  
AT: Identity crisis/loss of identity, Sexual stress, Social isolation, Infertility stigma, Depression, Reduced self-esteem  
CO: Depression, Decreased quality of life, Reduced self-esteem |
| Greil, McQuillan, et al. (2011) | RS\textsuperscript{QUANT} | ST: Fertility-specific distress  
AN: Infertility  
AT: Psychological stress, Financial stress, Social isolation, Infertility stigma, Increased anxiety, Depression, Reduced self-esteem  
CO: Increased anxiety, Depression, Reduced self-esteem |
### Table 1
Results of Literature Review for Infertility-Related Stress Concept Analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Type: RV, RS&lt;sup&gt;QUAL&lt;/sup&gt;, RS&lt;sup&gt;QUANT&lt;/sup&gt;, PS</th>
<th>Results from extracted conceptual properties: ST, AN, AT, CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greil, Shreffler, et al. (2011)</td>
<td>RS&lt;sup&gt;QUANT&lt;/sup&gt;</td>
<td>ST: Fertility-specific distress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AN: Infertility, Involuntary childlessness, Desire for parenthood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT: Psychological distress</td>
</tr>
<tr>
<td>Johnson and Fledderjohann (2012)</td>
<td>RS&lt;sup&gt;QUANT&lt;/sup&gt;</td>
<td>ST: Infertility distress, Fertility-specific distress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AN: Desire for parenthood, Involuntary childlessness, Infertility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT: Identity crisis/loss of identity, Psychological stress</td>
</tr>
<tr>
<td>Miles et al. (2009)</td>
<td>RS&lt;sup&gt;QUANT&lt;/sup&gt;</td>
<td>ST: Infertility distress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AN: Desire for parenthood, Infertility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT: Identity crisis/loss of identity, Social isolation, Infertility stigma, Increased anxiety, Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO: Increased anxiety, Depression</td>
</tr>
<tr>
<td>Mindes et al. (2003)</td>
<td>RS&lt;sup&gt;QUANT&lt;/sup&gt;</td>
<td>AN: Infertility, Desire for parenthood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT: Psychological stress, Social isolation, Infertility stigma, Depression, Reduced self-esteem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO: Depression, Reduced self-esteem</td>
</tr>
<tr>
<td>Newton et al. (1999)</td>
<td>RS&lt;sup&gt;QUANT&lt;/sup&gt;</td>
<td>AN: Infertility, Desire for parenthood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT: Sexual stress, Social isolation, Infertility stigma, Increased anxiety, Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO: Increased anxiety, Depression</td>
</tr>
<tr>
<td>Lauri A. Pasch et al. (2012)</td>
<td>RS&lt;sup&gt;QUANT&lt;/sup&gt;</td>
<td>AT: Increased anxiety, Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO: Increased anxiety, Depression</td>
</tr>
<tr>
<td>Peterson et al. (2007)</td>
<td>RS&lt;sup&gt;QUANT&lt;/sup&gt;</td>
<td>AN: Infertility</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT: Identity crisis, Sexual stress, Anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO: Anxiety</td>
</tr>
<tr>
<td>Quant et al. (2013)</td>
<td>RS&lt;sup&gt;QUANT&lt;/sup&gt;</td>
<td>AT: Psychological stress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO: Depression</td>
</tr>
<tr>
<td>Source</td>
<td>Type: RV, RS\textsuperscript{QUAL}, RS\textsuperscript{QUANT}, PS</td>
<td>Results from extracted conceptual properties: ST, AN, AT, CO</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Rich and Domar (2016) | PS | AN: Fear of the unknown, Infertility  
AT: Psychological stress, Financial stress  
CO: Infertility treatment dropout |
| Ridenour et al. (2009) | RV | ST: Infertility stress  
AN: Infertility  
CO: Depression, Reduced marital satisfaction |
CO: Increased anxiety, Depression, Infertility treatment dropout |
| Samadaee-Gelehkolae et al. (2015) | RV | AN: Infertility  
AT: Anxiety, Depression, Infertility stigma, Sexual stress  
CO: Decreased marital satisfaction, Anxiety, Depression, Reduced quality of life |
| Schneider and Forthofer (2005) | RS\textsuperscript{QUANT} | AN: Desire for parenthood, Fear of the unknown, Infertility  
AT: Social isolation, Infertility stigma, Reduced self-esteem, Financial stress  
CO: Reduced self-esteem |
| Whiteford and Gonzalez (1995) | RS\textsuperscript{QUAL} | AN: Desire for parenthood, Fear of the unknown, Involuntary childlessness  
AT: Identity crisis/loss of identity, Psychological stress, Financial stress, Social isolation, Infertility stigma, Depression, Reduced self-esteem  
CO: Depression, Reduced self-esteem |
AT: Identity crisis/loss of identity, Depression, Anxiety, Infertility stigma, Social isolation  
CO: Anxiety, Depression, Reduced quality of life |
Results

Antecedents

Antecedents are defined as being present in order for the concept to occur (Rodgers & Knafl, 2000). Infertility, primary or secondary, was recognized as a necessary antecedent for infertility-related stress (Boulet et al., 2017; Cousineau & Domar, 2007; Galst, 2018; Greil, McQuillan, et al., 2011; Greil, Shreffler, et al., 2011; Mindes et al., 2003; Ridenour et al., 2009). The American Society for Reproductive Medicine (ASRM, 2013) defines infertility as the inability to conceive or carry a pregnancy to term after 1 year of unprotected sex for those under the age of 35. For women 35 and over, this time is reduced to 6 months (Practice Committee of the American Society for Reproductive Medicine, 2013). Because of the distinction between women who identify as voluntarily childless (childless without intent) versus those who are involuntarily childless (childless with intent), the desire for parenthood was also recognized as an antecedent (Gerrity, 2001; Greil, Shreffler, et al., 2011; Johnson & Fledderjohann, 2012; Miles et al., 2009; Mindes et al., 2003; Newton et al., 1999; Schneider & Forthofer, 2005; Whiteford & Gonzalez, 1995). Additionally, fear of the unknown was commonly found in reviews, position statements, and qualitative literature,
presenting as the unpredictability of infertility with unknown treatment duration, success, or resolution (Cousineau & Domar, 2007; Galst, 2018; Rich & Domar, 2016; Schneider & Forthofer, 2005; Whiteford & Gonzalez, 1995). These fears significantly contributed to infertility-related stress (Wilson & Kopitzke, 2002).

**Attributes**

Attributes contain the defining characteristics of a concept (Rodgers & Knafl, 2000). During the literature review and analysis, several attributes were identified. Psychological burden appeared to be an overarching theme present in literature. Identity crises or loss of identity, as a woman, potential parent, and adult (Cousineau & Domar, 2007; Galst, 2018; Gerrity, 2001; Greil, 1997; Johnson & Fledderjohann, 2012; Miles et al., 2009; Mindes et al., 2003; Quant et al., 2013; Ridenour et al., 2009; Whiteford & Gonzalez, 1995), as frequently discussed in reviews and qualitative texts regarding infertility-related stress. The common practice of timing sexual intercourse with ovulation days to increase pregnancy chances can result in the loss of intimacy and spontaneity within a marriage (Cousineau & Domar, 2007; Gerrity, 2001; Newton et al., 1999; Ridenour et al., 2009). Sexual stress, identified by the inability to enjoy sex due to timed intercourse, was discovered in the literature as an attribute of infertility-related stress commonly experienced by couples (Cousineau & Domar, 2007; Galst, 2018; Gerrity, 2001; Greil, 1997; Newton et al., 1999; Peterson et al., 2007; Ridenour et al., 2009). Infertility treatments can take an enormous toll on the mental, physical, and financial health of those with infertility. Findings from the analysis suggest psychological stress and financial stress are attributes primarily as a result of the pursuit of assisted
reproductive therapy (Cousineau & Domar, 2007; Galst, 2018; Gerrity, 2001; Greil, McQuillan, et al., 2011; Johnson & Flederjohann, 2012; Rich & Domar, 2016; Rooney & Domar, 2018; Whiteford & Gonzalez, 1995). Social isolation from family and friends and infertility stigma were also determined to be shared attributes, as those with infertility felt isolated, out of place at family functions, and left behind as others achieved parenthood while they continued to struggle (Cousineau & Domar, 2007; Galst, 2018; Gerrity, 2001; Greil et al., 2010; Miles et al., 2009; Mindes et al., 2003; Newton et al., 1999; Ridenour et al., 2009; Schneider & Forthofer, 2005; Whiteford & Gonzalez, 1995). (Galst, 2018; Greil, McQuillan, et al., 2011; Miles et al., 2009; Newton et al., 1999; Lauri A. Pasch et al., 2012; Rooney & Domar, 2018), depression (Galst, 2018; Gerrity, 2001; Greil, 1997; Greil, McQuillan, et al., 2011; Miles et al., 2009; Mindes et al., 2003; Newton et al., 1999; Lauri A. Pasch et al., 2012; Ridenour et al., 2009; Rooney & Domar, 2018; Whiteford & Gonzalez, 1995), and reduced self-esteem (Gerrity, 2001; Greil, 1997; Greil, McQuillan, et al., 2011; Mindes et al., 2003; Schneider & Forthofer, 2005; Whiteford & Gonzalez, 1995), were identified as both attributes and consequences related to infertility-related stress.

**Consequences**

Consequences are defined as the downstream results of a concept (Rodgers & Knafl, 2000). Infertility-related stress has a large psychological component. Therefore, many of the identified consequences share this overarching element and are therefore similar to the attributes of the concept itself. Decreased quality of life (Boulet et al., 2017; Galst, 2018; Gerrity, 2001; Greil, 1997; Wilson & Kopitzke, 2002) and discontinuation of
infertility treatments related to overwhelming financial, physical, and emotional burdens (Cousineau & Domar, 2007; Galst, 2018; Rich & Domar, 2016; Rooney & Domar, 2018) were the most commonly identified consequences of infertility-related stress. Slightly less common, but still noteworthy, was reduced marital satisfaction as a result of sexual and financial strain (Galst, 2018; Gerrity, 2001; Newton et al., 1999; Samadaee-Gelehkolae et al., 2015). Increased anxiety (Galst, 2018; Greil, McQuillan, et al., 2011; Miles et al., 2009; Newton et al., 1999; Lauri A. Pasch et al., 2012; Rooney & Domar, 2018), depression (Galst, 2018; Gerrity, 2001; Greil, 1997; Greil, McQuillan, et al., 2011; Miles et al., 2009; Mindes et al., 2003; Newton et al., 1999; Lauri A. Pasch et al., 2012; Ridenour et al., 2009; Rooney & Domar, 2018; Whiteford & Gonzalez, 1995), and reduced self-esteem (Gerrity, 2001; Greil, 1997; Greil, McQuillan, et al., 2011; Mindes et al., 2003; Schneider & Forthofer, 2005; Whiteford & Gonzalez, 1995) were also identified as consequences related to social stigma, isolation, and loss of identity commonly experienced by those with infertility.

References

References for infertility-related stress include use in clinical and research settings. In clinic and hospital settings, the antecedents and attributes of infertility-related stress are used to help recognize potential impact and need for further evaluation of patients presenting with increased psychological distress, such as increased anxiety and depression (Cousineau & Domar, 2007; Gerrity, 2001; Greil, 1997; Rich & Domar, 2016; Ridenour et al., 2009). In research settings, the concept of infertility-related stress is used to aid investigators in identifying patients under increased levels of stress together with
empirical referents measuring infertility stress and quality of life, such as the Fertility Quality of Life (FertiQoL) questionnaire, the Fertility Problem Inventory, and SCREENIVF (Greil, 1997; Newton et al., 1999; Peterson et al., 2007; Rich & Domar, 2016). The FertiQoL tool is a self-report questionnaire measuring fertility-specific quality of life by assessing treatment-related quality of life, core quality of life, and physical health of infertility patients (Boivin et al., 2011). It is also advantageous for clinicians seeking to separate the effects of infertility stress versus treatment-related infertility stress. The Fertility Problem Inventory is a self-report questionnaire that can assist clinicians and researchers in examining the impact of infertility-related stress in patients (Newton et al., 1999). This is done by using a global score from a combined five domains determined to be most relevant to patients with infertility: (1) social concern, (2) sexual concern, (3) relationship concern, (4) need for parenthood, and (5) rejection of a childfree lifestyle (Newton et al., 1999). The SCREENIVF questionnaire can be used by clinicians to screen and identify patients at risk for emotional maladjustment and offer them additional support but is only indicated for use before starting assisted reproductive treatments (Ockhuijsen et al., 2017). Screening results provide an at-risk score based on responses to five factors: (1) anxiety, (2) depression, (3) social support, (4) helplessness, and (5) acceptance (Ockhuijsen et al., 2017).

Exemplar

Following Rodgers' method of concept analysis, case studies exemplifying the concept of infertility-related stress were identified in the literature (Rodgers & Knafl, 2000). In their analysis of the infertility experience, Whiteford and Gonzalez (1995)
provided an in-depth exploration of the hidden burdens of infertility experienced by four women. Though each woman suffered from different diagnoses, such as endometriosis, unexplained infertility, damaged fallopian tubes, and irregular ovulation, their stories shared common elements. Women experienced stigma, social isolation, anxiety, depression, marital strain, and loss of identity as a part of infertility. Although the case studies presented by Whiteford and Gonzalez focused primarily on the lack of outward expressions of disease or disability that further perpetuate infertility stigma, the overarching theme of infertility-related stress and psychological strain experienced by participants was undeniable and highlights the importance of addressing infertility-related stress.

Discussion

This concept analysis defined the characteristics, antecedents, and consequences of infertility-related stress. From the literature review and analysis, a proposed definition of infertility-related stress is an overwhelming mental, emotional, or physical stress resulting from the desire, but inability, to conceive children and/or from coinciding infertility treatments. This can be characterized by identity crises or loss of identity as a woman and potential parent, inter-relational strain, perceived social isolation and stigma, anxiety, depression, and reduced self-esteem. This definition may be used to aid in the recognition of this concept and refer women for more specialized care to reduce the stress that accompanies infertility and infertility treatments.

Although only three databases were utilized for this concept analysis, there appears to be a saturation of both qualitative and quantitative studies on the psychological
effects of infertility and infertility-related stress. However, many of them fail to provide a complete picture of what constitutes infertility-related stress. This analysis aimed to fill that gap. Many of the studies focused solely on women who were pursuing infertility treatments. A gap was noted in the current research regarding how women with infertility who chose not to pursue assisted reproductive treatments experience infertility-related stress. Another consideration includes the accuracy of self-report questionnaires. These measures have potential to be unintentionally skewed due to patients not wanting to appear depressed or anxious. Additional studies should explore the use of stress biomarkers in combination with questionnaires to reduce the potential for self-report bias.

A limitation of some of the previous studies on infertility and stress is the reliance on cross-sectional data collection. However, psychological outcomes, such as depression and anxiety, may be temporally influenced depending on when these studies occur within an assisted reproduction cycle (e.g., hopeful at the beginning of the cycle, anxious during the 2-week wait, or depressed immediately following a failed cycle) or by medications taken during assisted reproduction cycles (Boivin & Takefnan, 1996; Rooney & Domar, 2018; Wilson & Kopitzke, 2002). The longitudinal use of daily self-report questionnaires, completed via text messaging prompts, could provide a more comprehensive, real-world, just-in-time report of the mental health and reproductive cycle fluctuations experienced by women with infertility and potentially reduce recall biases.

Limitations of this concept analysis included the exclusion criteria and the chosen sample setting. Due to differing cultural values and beliefs surrounding infertility, only studies based on US populations were included in the current analysis. This limits generalizability for women suffering from infertility who identify with cultures and
beliefs other than those most commonly found in the US. Clinicians intending to utilize the concept of infertility-related stress when working with women from non-US-based cultures should take into consideration additional attributes and consequences that patients may experience based on social and cultural influences. Additionally, in contrast to countries with universal health care that mandates coverage of infertility treatments, patients in the United States rarely have insurance coverage and most incur substantial out-of-pocket costs for infertility treatments. Therefore, financial aspects may play a larger role in infertility-related stress in the United States when compared with other countries. Moreover, while three databases were used to search literature, other databases may yield additional results. Further research should include the addition of supplementary databases to ensure complete identification of all literature, antecedents, attributes, and consequences of infertility-related stress.

**Conclusion**

This analysis explored the concept of infertility-related stress by means of identifying antecedents, attributes, and consequences within the available literature using Rodgers' evolutionary method of concept analysis. Infertility-related stress involves psychological strain that can accompany the inability to conceive or carry a child and/or psychological strain resulting from assisted reproductive therapy. The desire to have children must also coincide with infertility as an antecedent. Fear of the unknown, although not required, often precedes infertility-related stress as unknown treatment duration, infertility duration, or outcomes. Defining attributes include loss of identity, inter-relational and sexual strain, psychological stress, financial stress, and social
isolation and stigma. Consequences include decreased quality of life, treatment dropout, and reduced marital satisfaction. Anxiety, depression, and reduced self-esteem can be characterized as both attributes and consequences. As evidenced by the literature, infertility-related stress impacts many women who deal with infertility, yet previous studies fail to provide a clear definition of the concept. Future research should focus on discovering whether a difference exists between patients who pursue treatments versus those who do not.

**Relevance to Clinical Practice**

Clarification of the concept of infertility-related stress has potential to provide clinicians with a more thorough understanding of precursors, symptoms, and possible consequences. This facilitates early identification of patients in need of additional support. Results from this concept analysis enhance the understanding of infertility-related stress that can lead to improved recognition and mitigation of symptoms with the potential to improve patients' quality of care and ultimately their quality of life.
Continuation of Chapter 2 - Integrative Review of the Literature

**Impact of Psychological Distress on Assisted Reproduction**

Several studies have attempted to clarify whether an association truly exists between psychological distress, like stress, anxiety, and depression, and ART outcomes of clinical pregnancy and live birth rates. Thus far, no clear and direct connection has been established between depression prior to ART and clinical pregnancy (Aimagambetova et al., 2020; Cheung et al., 2019; Maroufizadeh et al., 2019; L. A. Pasch et al., 2012; Peng et al., 2021; Xu et al., 2017) or live birth rates (L. A. Pasch et al., 2012). For the most part, no association between anxiety and clinical pregnancy rates (Cheung et al., 2019; Hashemi et al., 2012; Maroufizadeh et al., 2019; L. A. Pasch et al., 2012; Peng et al., 2021; Xu et al., 2017) or live birth rates (L. A. Pasch et al., 2012) or between stress and clinical pregnancy rates (Cheung et al., 2019; Maroufizadeh et al., 2019; Peng et al., 2021) have been found. However, conflicting evidence suggests that anxiety and stress may play a role in IVF outcomes, with some studies indicating a potential correlation between increased stress (Aimagambetova et al., 2020; Turner et al., 2013) or increased anxiety (Turner et al., 2013) and clinical pregnancy rates. Based on the current evidence, depression seems to have no significant effects on pregnancy and live birth rates, but it is still unclear whether increased anxiety or stress levels negatively impact IVF success.
Attending to Psychological Distress

Mental Health Care and the Infertility Clinic

Despite provider awareness about the psychological impact of infertility and the perception held by various providers that psychological distress may influence treatment outcomes, a recent study indicated that most providers do not formally screen for anxiety or depression (Hoff et al., 2018). Patient-focused studies provide further validation by indicating that although patients desire more psychological care and related resources (Dawadi et al., 2018; Domar et al., 2018; El Kissi et al., 2013), the vast majority of health care providers are not offering any (Dawadi et al., 2018). Unfortunately, failing to provide information and access to psychological care and resources has shown to be detrimental. Female patients with infertility who suffer from depression and psychological distress are more likely to discontinue infertility treatments, even when they have insurance coverage (Domar et al., 2018; Pedro et al., 2017). Consequently, patients who remain involuntarily childless long-term can experience further exacerbations of anxiety, stress, and depression, struggle with feelings of loss, grief, and hopelessness, and feel as though they have lost purpose in their lives, leading to a prolonged grief disorder (Fieldsend & Smith, 2020; Naab et al., 2019). Simply ensuring that patients are screened for psychological distress early on and have easily accessible mental health resources may alleviate further distress caused by infertility and diminish the likelihood of patients prematurely discontinuing infertility treatments that further exacerbates poor psychological health (Dawadi et al., 2018; Domar et al., 2018).
Treatments for Reducing Anxiety, Stress, and Depression

Psychological interventions, including traditional psychotherapy and complementary methods like acupuncture and yoga, have been proposed to help alleviate the emotional burden of infertility, with the vast majority using mindfulness or mind-body approaches. Group mindfulness sessions have shown to reduce depression (Faramarzi et al., 2013; Galhardo et al., 2013; Mousavi et al., 2020; Nery et al., 2019; Psaros et al., 2015), anxiety (Chan et al., 2012; Kim et al., 2014; Mousavi et al., 2020), and stress symptoms (Bakhtiyar et al., 2019; Chan et al., 2012; Nery et al., 2019; Psaros et al., 2015), with one study touting long-term maintenance effects on reducing depression after seven years (Galhardo et al., 2019). Individual sessions used slightly different approaches with personalized therapy or e-therapy sessions (Heredia et al., 2020; Koszycki et al., 2012; van Dongen et al., 2016), internet-based mind-body sessions (Clifton et al., 2020), or comparing the effects of mindfulness practice to gratitude journaling (Bai et al., 2019). However, the individual sessions did provide similar results by decreasing depression (Bai et al., 2019; Clifton et al., 2020; Koszycki et al., 2012), anxiety (Clifton et al., 2020; Heredia et al., 2020; Koszycki et al., 2012; van Dongen et al., 2016), stress (Clifton et al., 2020), and even pregnancy rates (Clifton et al., 2020). Only one study indicated conflicting results with mindfulness therapy failing to provide any significant effect on anxiety or stress and gratitude journaling resulting in no improvements on any variable with a potentially negative impact on stress and anxiety (Bai et al., 2019). Group sessions ranged from four to ten weeks, while individual approaches spanned anywhere from one 90-minute session up to 12 weeks of individual sessions. Both group and individual approaches show notable potential for decreasing the
adverse psychological effects of infertility and should be considered part of a regular holistic infertility care regimen.

Complementary approaches for psychological interventions have included randomized control trials assessing the utility of music therapy (Aba et al., 2017), expressive writing (Frederiksen et al., 2017), or acupuncture (Guven et al., 2020) to improve anxiety and depressive symptoms, reduce stress and infertility distress, and improve pregnancy rates with some success. Music therapy and acupuncture both reduced anxiety and resulted in minor increases in pregnancy rates, with acupuncture showing significantly increased pregnancy and live births rates (Aba et al., 2017; Guven et al., 2020). Expressive writing showed minimal effectiveness with nonsignificant decreases in depression and anxiety and nonsignificant increases in infertility stress and pregnancy rates, possibly due to an inadequate sample size for the trial (Frederiksen et al., 2017). Alternatively, hatha yoga displayed favorable results, with participants reporting improvements in anxiety and depression (Valoriani et al., 2014) and reductions in infertility-related stress (Oron et al., 2015; Valoriani et al., 2014).

**Summary**

The state of the science of mental health and infertility is primarily dominated by quantitative literature that focuses on anxiety, depression, and infertility stress. Findings suggest that many women suffer from depression and anxiety, often as co-morbidities, and high levels of infertility-related stress. While many researchers have used the same instruments to detect psychological variables, there is still a significant need to standardize these measurements in women with infertility. This would allow meta-
analyses to provide more clearly defined incidence rates and risk factors of depression and anxiety among individuals with infertility. Conflicting evidence suggests that there may be an association between anxiety and stress with ART outcomes but not between depression and ART outcomes. However, unresolved infertility resulting in long-term childlessness places women at an increased risk for chronic trajectories of depression and anxiety, and a higher risk for suicide.

Although quantitative measurements have provided ample support for the presence of psychological distress, anxiety, depression, and infertility-related stress in patients with infertility, they leave us with little understanding of the day-to-day psychological impact of infertility. Meanwhile, individuals have consistently voiced their desire for more access to psychological care and resources during infertility. Mind-body, mindfulness, and traditional psychotherapy interventions targeted for infertility-related symptoms have shown promising results in reducing psychological burden. However, even though clinicians are aware of the need to identify patients and reduce the psychological burden during infertility, they consistently fail to screen patients for mental health, suggesting a gap in knowledge regarding the mental health of women during infertility still exists.

Chapter 2 Summary

Chapter two presented an overview of the current state of the science of infertility and mental health and how infertility affects women with DOR. This chapter supported the need for further inquiry into the lived experience of young women with DOR by presenting the epidemiologic basis of DOR and an analysis of the current literature. This
review highlights the multifaceted concepts of infertility caused by DOR and mental health. Women with DOR can be challenging to identify, counsel, and successfully treat with various risk factors and causes, poor responses to ART, and poorer reproductive outcomes than other infertility etiologies. Many also cope with mental health consequences caused by infertility and an unexpected diagnosis. In addition, clinicians face treatment-related challenges with a lack of professional consensus on the definition and diagnostic criteria for DOR and potential for long-term physical health consequences, indicating a dire need to understand the DOR diagnosis better. Infertility causes significant psychological distress, most commonly depression, anxiety, and infertility-related stress. However, clinicians and researchers have chosen no gold standard to examine these states in those with infertility, thereby reducing the ability to clearly define incidence rates and risk factors. While current evidence suggests that anxiety and stress may influence ART outcomes, thus far, depression has not been shown to effect either ART or pregnancy outcomes in women with infertility.

Psychological interventions have shown promising results in reducing the emotional distress of patients with infertility. However, without identifying patients needing assistance through regular clinic screenings, many patients fail to receive the mental health resources and services they need and desire. Consequently, patients with unaddressed mental health concerns or unresolved infertility are at a higher risk for chronic depression, anxiety, and suicide. Early identification and treatment of individuals with anxiety, depression, or a history of other psychiatric disorders can reduce the chances of delayed and chronic trajectories of anxiety and depression, thus reducing the potential for long-term mental health disorders caused or exacerbated by infertility.
Focusing psychotherapeutic interventions on building resiliency and positive coping skills would provide individuals and couples with the skills necessary to manage their mental health when facing the uncertain outcomes of infertility.
References


CHAPTER 3

A REVIEW OF THE PSYCHOMETRIC PROPERTIES AND IMPLICATIONS FOR THE USE OF THE FERTILITY QUALITY OF LIFE TOOL

by

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PAPER 2
A REVIEW OF THE PSYCHOMETRIC PROPERTIES AND IMPLICATIONS FOR THE USE OF THE FERTILITY QUALITY OF LIFE TOOL

ABSTRACT

Objectives: To analyze and synthesize the reported psychometric properties of the Fertility Quality of Life (FertiQoL) instrument and describe its implications for use in practice and research in men and women with infertility.

Methods: A systematic literature search was performed to identify all articles using the FertiQoL tool. PubMed, CINAHL, and PsycINFO were searched from September 2006 through May 2022. Studies were eligible for inclusion if they reported psychometric data on the original FertiQoL tool using a sample population of individuals with infertility. Sample size, country of origin, and psychometric data were documented for each study.

Results: The initial search revealed 153 articles that had utilized the FertiQoL. Following abstract, title, and full-text screenings, 53 articles reported psychometric data and met criteria for inclusion. The FertiQoL is a sound measurement with satisfactory reliability and validity. Studies indicated adequate reliability in the overall scale ($\alpha = 0.78–0.94$), as well as the core Emotional, Mind/Body, Social, and Relational scales ($\alpha = 0.43–0.92$) and two optional Tolerability and Environment fertility treatment subscales ($\alpha = 0.67–0.91$). Although the Relational subscale exhibited slightly lower reliability in several studies, the internal consistency for the measurement as a whole was satisfactory. Results also indicate adequate: 1) face and content validity with extensive professional and patient feedback during development; 2) convergent validity with general quality of life, depression, and anxiety measurements; and 3) structural validity using both confirmatory and exploratory factor analyses.
Conclusion: The FertiQoL tool is the most commonly used instrument to measure the impact of fertility issues on quality of life in men and women with infertility. Understanding the impact of infertility on quality of life provides valuable insight into the areas of infertility-related care that need to be prioritized, such as mental health or relational stressors. While the instrument has been used in different patient populations with infertility and available in multiple translations, it is necessary to understand the updated psychometric properties and the implications for its use. This review shows that the FertiQoL is reliable and valid for cross-cultural use among individuals with various etiologies of infertility.

Keywords: infertility, quality of life, systematic review, psychometrics
A REVIEW OF THE PSYCHOMETRIC PROPERTIES AND IMPLICATIONS FOR THE USE OF THE FERTILITY QUALITY OF LIFE TOOL

Introduction

Between 2006 and 2010, prevalence studies estimated that approximately 72–186 million individuals worldwide were affected by infertility [1, 2], a reproductive disease that results in the inability to conceive after 12 months of unprotected sex [3, 4]. Despite the immense number of individuals that are affected globally, the vast social, physical, and mental health implications of infertility have been largely unaddressed in the last 15 years [5]. Infertility can be female-specific, male-specific, or a combination of various factors and etiologies [6]. Female-specific factors can include endometriosis, diminished ovarian reserve, and polycystic ovarian syndrome [6], while male-specific infertility can evolve from poor sperm quality, quantity, or medical comorbidities [7].

Regardless of the etiology, individuals and couples with infertility face significant infertility-related stress stemming from life-changing decisions regarding their path to parenthood or to remain childless. Individuals with infertility report symptoms of anxiety and depression at rates between 25 and 60%, similar to those with chronic health conditions [8], while approximately 2.7–9.5% of individuals in the general population experience anxiety and depression [9,10,11,12]. In addition to the psychological distress of infertility, financial burdens of infertility treatments and patient comorbidities can further limit reproductive options, further compounding infertility-related stress and...
creating additional barriers to parenthood [13]. Previous studies on infertility-related mental health have historically focused on general infertility or those pursuing assisted reproductive technologies (ART). However, the mental health of subpopulations of people with infertility, such as individuals who choose not to or cannot afford to pursue ART, those with non-anatomical causes of infertility, such as diminished ovarian reserve, or those with iatrogenic infertility following radiation and chemotherapy treatments for cancer, have been largely understudied.

Understanding the impact of infertility on quality of life provides valuable insight into the areas of infertility-related care that need to be prioritized, such as mental health or relational stressors. Three of the most commonly utilized instruments for assessing patient-reported outcomes related to fertility quality of life include the Fertility Problem Stress (FPS) questionnaire [14], the Fertility Quality of Life (FertiQoL) questionnaire [15], and the Fertility Problem Inventory (FPI; [16]).

The FPI is a self-report questionnaire that examines the impact of infertility-related stress in individuals with infertility. The FPI provides a global score by combining five domains determined to be most relevant to those with infertility: 1) social concern, 2) sexual concern, 3) relationship concern, 4) need for parenthood, and 5) rejection of a childfree lifestyle [16]. The FPI is available in 11 languages and contains 46 questions, but is currently only available in paper format, requiring an administrator to convert the survey into an electronic format using survey software, if desired [17]. Alternatively, the FPS is a self-report questionnaire with only 14 items [14]. While the participant burden may be lower compared to FPI with fewer questions to answer, the FPS is also limited to a paper format that would require electronic conversion, and has only been translated into
two languages. Neither the FPI nor the FPS creators have reported data on the instrument validation process, or have indicated that input from infertile patients was sought during the development of their measures [17]. In addition, rather than assessing the impact of infertility on a person’s quality of life, these measures focus on the concept of infertility-related stress. The FertiQoL questionnaire is currently the most widely used instrument for measuring fertility quality of life in individuals with infertility. However, there has been a sharp increase in the number of studies utilizing the FertiQoL instrument in the last several years. An updated review is needed to provide researchers and providers with the most current evidence on the utility and soundness of the FertiQoL. This review aims to analyze and synthesize the reported psychometric properties of the FertiQoL instrument and describe implications for its use in practice and research.

**Methods**

**Search Strategy**

A literature search was performed to identify research studies that used the FertiQoL questionnaire. The search was completed on May 4th, 2022, using PubMed via the National Library of Medicine, CINAHL through the EBSCOhost platform, and PsycINFO using ProQuest. No additional articles were identified through hand-searching article reference lists using the ancestry approach. No date restrictions were placed on the search to ensure all studies utilizing the FertiQoL were included. However, results included articles published from September 2006 through April 2022. The search strategy for all three databases included keywords “fertility quality of life,” “FertiQoL,” and “fertility-related quality of life,” and application of the “English” filter. Inclusion criteria
included: 1) primary research studies; 2) sample population of individuals or couples with infertility; 3) and psychometrics reported on the original FertiQoL instrument. Articles were excluded for the following criteria: 1) secondary research studies or reviews and 2) studies using a modified version of the FertiQoL instrument.

**Results**

One hundred thirty-two articles were initially retrieved from PubMed, 77 from CINAHL, and 45 from PsycInfo, for a total of 254 results. After the removal of 101 duplicates, 153 articles were available to screen. Following title and abstract screening, 26 articles were excluded, leaving 127 for review. Following the inclusion and exclusion criteria, 74 articles were excluded. Sixty-five articles did not report any psychometric properties of the FertiQoL questionnaire in their study sample, four were not empirical research studies (reviews and books), three were only published as abstracts, one included the use of an ineligible patient population, and one did not use the FertiQoL to measure fertility quality of life. Fifty-three articles were ultimately included in the current review. (See Fig. 1 for PRISMA diagram).
The majority of the articles collected data using a paper version of the FertiQoL instrument \((n = 29)\), followed by online collection \((n = 10)\), or a combination of paper and online data collection methods \((n = 6)\). Eight articles did not specify whether data collection was completed using the paper or online version. Thirty-three studies were conducted using a female sample, two were male-specific, 11 were female and male dyads, and seven were uncoupled males and females, with an average age of 34.3 across all studies. Twenty-one countries were represented in the study results, with 19 studies
originating from East Asia, 18 from Europe, 11 from the Middle East, 7 from North America, and one each from Australia and New Zealand. Additionally, six studies were multisite studies with participants from more than one country. See Fig. 2 for a map of countries represented.

**Figure 2**
Global Disbursement of Participants


**Fertility Quality of Life Tool Development**

The FertiQoL was published in 2011 as a 36-item self-report questionnaire designed to measure the impact of fertility problems on quality of life in both men and women suffering from infertility [15]. The development of the FertiQoL was a collaborative effort among the European Society for Reproductive Medicine, the American Society for Reproductive Medicine, and Merck-Serono. It was led by 1) psychology professor and researcher, Jacky Boivin; 2) clinical health psychologist and assistant professor, Janet Takefman; and 3) clinical professor and psychologist, Andrea Braverman [18]. Two questions rate overall quality of life and physical health, 24 core questions assess the impact of infertility on quality of life, and an optional treatment-specific module contains 10-questions for participants pursuing infertility treatments [19]. While it is condition-specific (infertility), it is not specific to underlying causes of infertility, such as endometriosis or polycystic ovarian syndrome. It is acceptable for use in both men and women experiencing infertility, those pursuing treatment, and those who are not. Except for the optional treatment section, the FertiQoL is a static measurement where everyone completes the same number of questions [19, 20].

While no theoretical framework was specified for the development of the FertiQoL, authors mirrored the development protocol of the World Health Organization Quality of Life (WHOQOL) measure that emphasizes quality of life as a multidimensional concept consisting of a person’s perception of their physical and psychological health, level of independence, social relationships, environment, and personal beliefs [15, 21]. The FertiQoL was designed using classical test theory in collaboration with international psychosocial experts in reproductive health and a steering
committee [15]. After conducting a literature review to generate an initial pool of 302 items dispersed among 14 domains, the pool was then reduced to 116 items after eliminating redundant and irrelevant items. Seventeen focus groups in five countries were conducted with infertility patients, excluding an additional 14 items, for a total of 102 items. The feasibility and acceptability survey exposed any problematic questions, and the item pool was reduced to the final measurement structure: 24 core items, two overall health items, and ten optional treatment items [15]. Psychometric evaluations, exploratory factor analyses, and factor loadings of the items revealed mostly high reliability and sensitivity for both the subscales and the total scales [15].

**Data Collection and Scoring**

The FertiQoL self-report questionnaire is available in both paper and electronic formats. While free to administer, no alterations can be made to the questionnaire, and creators should be acknowledged in any publication [22]. Scores, sample size, means, and standard deviations should be sent to the FertiQoL authors for publication on their website [22]. The paper format is available in 48 languages, and the electronic is available in 11. The only instructions necessary for completing the survey are: 1) select the response that most reflects how you feel in your current thoughts and feelings, and 2) only complete the questions with an asterisk if you have a partner [19].

Overall, minimal training is required to administer and score the FertiQoL questionnaire. Scoring is automatic when completing the FertiQoL online. Participants can provide a clinic name, identification number, and email address where they would like the results sent. Alternatively, scores must be computed manually or using an Excel
algorithm when administering the paper format, with five core and two treatment questions requiring reverse scoring before scaling the raw subscale and total scores. There are two Excel options for scoring the FertiQoL: 1) the researcher can manually enter scores for each participant into the corresponding question box and score it themselves, or 2) scores can be entered for each question, with the Excel algorithm providing the raw and scaled subscale and total scores for each person. Individuals collecting and processing survey data need a basic understanding of Excel and its functions, mainly the ability to input scores into correlating boxes. If participants complete the online version and provide an email address, the results obtained from the online FertiQoL will also be delivered electronically to their email in Excel format. Participant data can then be combined into one Excel datasheet to view answers to individual questions, subscale scores, and total scores within one file.

There are certain risks to privacy that could be encountered when completing the FertiQoL online because individuals are required to provide initials, date of birth, country of residence, and gender, increasing the ability to identify a participant. Without specific protocols preventing the collection of internet protocol (IP) addresses with an electronic survey, individuals may be at an increased risk of privacy breach. However, survey results can be de-identified and protected once data collection is complete. Because of the risk of privacy breach, individuals should be made aware of the measures taken by researchers and clinicians to protect their identity and personal health information.

Scoring the complete FertiQoL, including the optional treatment module, produces six subscales and three total scores [23]. The subscales include four scales with six questions each (Emotional, Mind/Body, Relational, and Social) and an optional
module with two subscales looking at environment and treatment tolerability with four and six questions each, respectively. The four required scales comprise the Core FertiQoL score, while the two optional scales make up the Treatment score. These two scores combine to provide the total quality of life score.

Items are measured as continuous variables on a Likert scale that produces a value between zero and four. Likert scale options include very poor (0) to very good (4), always (0) to never (4), and an extreme amount (0) to not at all (4), with some items requiring reverse scoring [23]. Values are summed and scaled to provide subscale and total scores. Both total and subscale scores range from zero to 100, with higher scores indicating better quality of life. While scores are left to interpretation because of a lack of guidelines, the instrument creators provide access to a compilation of published means and standard deviations of total and subscales scores using the FertiQoL tool [24].

**Validity**

Validity is the ability of an instrument to accurately measure a construct that it intends to measure [20]. The three main types of validity are content and face validity, criterion validity, and construct validity, with each consisting of several aspects. Criterion validity refers to the degree that scores on a focal measurement adequately reflect that of a gold standard [20, 25]. Since there is currently no gold standard measurement for infertility specific quality of life, criterion validity has not been measured for the FertiQoL and will not be addressed in this review. Rather, this review will report on the content and face validity and construct validity of the FertiQoL.
**Face and Content Validity**

Face and content validity are subjective evaluations that ensure an instrument reflects the construct it intends to measure [20]. Providers and patients can assess face validity to ensure that an instrument appears to measure its intended construct. Face validity is often critical when developing disease-specific measurements, like the FertiQoL, because general measures may not seem relevant to participants, reducing the potential for completion and accuracy of a generalized tool [20, 25]. Alternatively, content validity is usually assessed by field experts, like clinicians and researchers, that ensure the entire construct is being measured [20].

The development of the FertiQoL instrument included extensive integration of results from several focus groups and debriefings comprised of the FertiQoL steering committee and psychosocial reproductive health experts from 11 countries (psychologists, counselors, social workers, researchers, patient user groups, physicians, and nurses), alongside individuals with infertility, where questionnaire items were assessed and deemed both relevant and comprehensive [15, 17]. Vital feedback from the focus groups and debriefings improved face and content validity by correcting wording and eliminating redundant items. An acceptability and feasibility study was also conducted and included 525 participants in 10 countries, with results further supporting prior assertions of face validity and acceptability by individuals with infertility [15].

**Construct Validity**

**Convergent validity.** Convergent validity is the degree to which scores on a measurement correlate with scores on a measure with which there is a hypothesized relationship
However, in the absence of a “gold standard” measurement, like fertility-specific quality of life, instruments assessing constructs with expected conceptual convergence, like general quality of life, relational satisfaction, anxiety, and depression, may be used instead [20]. To assess convergent validity using a generic quality of life instrument, Heredia et al. [26] used Spearman’s rho ($\rho$) to measure correlations between the Short Form 36 (SF36) questionnaire for general physical and mental health and the FertiQoL, whereas Hekmatzadeh et al. [27] used the shorter adaptation of the instrument, the 12-item Short Form Health Survey (SF-12) and Pearson’s $r$. Correlations were considered weak ($<.3$), moderate ($\geq.3<.7$), or strong ($\geq.7$), and statistically significant at $p > 0.05$.

The Core and Total scores of the FertiQoL were moderately positively associated with social functioning and mental health subscales of the SF-36 [26]. Both instruments (SF-12 and SF-36) exhibited agreement with moderate positive correlations between the FertiQoL Emotional subscale and mental health, role limitations from emotional problems, and vitality. Additionally, the SF-36 indicated a moderate positive correlation with social functioning. However, the FertiQoL Social and Mind/Body subscales showed more correlational variability with the two adaptations of the Short Form Health Survey, with the SF-12 exhibiting stronger convergence with the FertiQoL Social subscale and between the Mind/Body subscale and physical problems than the SF-36. More specifically, results from the SF-12 indicated a moderate positive correlation between the Social subscale of the FertiQoL and the social functioning domain ($r = 0.49$, $p < 0.001$), while the SF-36 found no significant correlation with the social domain ($\rho = 0.117$), but rather, a moderate positive correlation between the FertiQoL Social subscale and the SF-
general health domain ($\rho = 0.360, p < 0.05$). Additionally, there was a moderate positive correlation between the Mind/Body subscale and role limitations from physical problems ($r = 0.47, p < 0.001$) and physical functioning ($r = 0.68, p < 0.001$) with the SF-12, but no significant correlations were found with physical functioning ($\rho = 0.080$), physical role limitations ($\rho = 0.127$), or bodily pain ($\rho = 0.256$) on the SF-36. However, results did suggest moderate correlations between the Mind/Body subscale and social functioning ($\rho = 0.497$), mental health ($\rho = 0.524$), vitality ($\rho = 0.417$), and emotional role ($\rho = 0.417$) on the SF-36. Although the two studies vary in correlational significance on certain subscales, overall results provide evidence of adequate convergent validity between measurements of general quality of life and the disease specific FertiQoL.

Since depression and anxiety are two well-known consequences of infertility, the Hospital Anxiety and Depression Scale (HADS; [28]) is often used to confirm convergent validity using correlation coefficients [29]. It has been utilized in multiple populations, including Iranian [27, 30], Turkish [31, 32], and Dutch women with infertility [33]. As hypothesized, significant negative correlations were found between the core total and subscales of the FertiQoL and HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D) scales, with fertility quality of life increasing as depression and anxiety decrease. Weak to moderate associations have been found between the Relational subscale and the HADS-A ($r = -0.2 – -0.49$) and HADS-D ($r = -0.32 – -0.50$). Similar results have been found between the Relational subscale and multiple measurements of relationship quality. In a validation study, Donarelli et al. [34] found weak to moderate positive correlations between the FertiQoL Relational subscale and marital satisfaction ($\rho = 0.31–0.36$) and dyadic adjustment ($\rho = 0.28–0.31$), while moderate negative
associations were found with sexual stress ($\rho = -0.48$) and marital commitment ($\rho = -0.30$ – $-0.37$). All other core subscales had moderate correlations with anxiety and depression. Moderate correlations exist between the core total and HADS-A ($r = -0.56$ – $-0.64$) and HADS-D ($r = -0.51$ – $-0.67$). Moderate correlations were reported for the Mind–Body subscale with the HADS-A ($r = -0.48$ – $-0.65$) and HADS-D ($r = -0.38$ – $-0.66$), the Social subscale with the HADS-A ($r = -0.44$ – $-0.55$) and HADS-D ($r = -0.46$ – $-0.56$), and the Emotional subscale with the HADS-A ($r = -0.50$ to -0.62) and HADS-D ($r = -0.49$ to -0.54). See Table 1 for a summary of correlation coefficients from the studies reporting on the HADS and FertiQoL convergent validity.

**Table 1**
Pearson's correlations between FertiQoL and HADS

| FertiQoL Subscales | HADS-Anxiety | | | | | HADS-Depression | | | | |
|-------------------|--------------|--------------|--------------|--------------|--------------|----------------|--------------|---|--------------|---------------|-------|--------------|---------------|-------|
| CORE              | MB           | REL          | SOC          | EMO          | CORE         | MB             | REL          | SOC | EMO          | |                |                  | |
| Aarts, van Empel [33] | -0.64**     | -0.65**      | -0.29**      | -0.48**      | -0.58**      | -0.67**        | -0.66**      | -0.37** | -0.54** | -0.54** | -0.64* | -0.65* | -0.27* | -0.44* | -0.56* | -0.65* | -0.65* | -0.35* | -0.52* | -0.51* |
| Dural, Yasa [32] | -0.62* | -0.64* | -0.27* | -0.44* | -0.56* | -0.65* | -0.65* | -0.35* | -0.52* | -0.51* |
| Kahyaoglu Sut and Balkanli Kaplan [31] | -0.56*** | -0.48*** | -0.20 ns | -0.45*** | -0.62*** | -0.51*** | -0.38*** | -0.32* | -0.46*** | -0.49*** |
| Maroufizadeh, Ghahei [30] | -0.63*** | -0.58*** | -0.49*** | -0.55*** | -0.50*** | -0.66*** | -0.62*** | -0.50*** | -0.56*** | -0.53*** |

FertiQoL subscales: CORE Core total, MB Mind/Body, REL Relational, SOC Social, EMO Emotional, ns not significant

*P < 0.05, **P < 0.01, ***P < 0.001

**Structural validity.** Structural validity is a measurement of how well an instrument captures the hypothesized dimensionality of a complex construct using multiple subscales [20]. Structural validity is most commonly assessed using confirmatory factor analyses (CFA) or exploratory factor analyses (EFA). During the development of the FertiQoL, authors used EFA to explore subscale structure and
corroborate the conceptual model [15, 20]. Aside from Hekmatzadeh et al. [27], subsequent studies used CFA to assess structural validity [20]. Donarelli et al. [34] reported a CFA using chi-square, comparative fit (CFI), goodness of fit (GFI), and root mean square error of approximation (RMSEA) indices for the FertiQoL with a good fit for the four-factor model and Relational subscale in 589 infertile Italian men and women. Maroufizadeh et al. [30] also used CFA, reporting chi-square, CFI, RMSEA, and standardized root mean square residual indices to determine goodness of fit of the Persian FertiQoL using a sample of 155 infertile Iranian women. Both studies confirmed goodness of fit with acceptable factor loadings on all items except for one question asking whether infertility had strengthened partner commitment [30, 34]. Alternatively, Hekmatzadeh et al. [27] confirmed the six underlying factors present in the complete Iranian version of the FertiQoL tool (Emotional, Mind/Body, Relational, Social, Environmental, and Tolerability) with a sample of 300 women with infertility in Iran. Results from the EFA with principal component factor analysis indicated all factor loadings were greater than 0.30 and all original questions remained. The FertiQoL has demonstrated structural validity, with studies confirming that the subscales adequately reflect the hypothesized underlying factors.

**Reliability**

Reliability refers to a measurement's ability to provide consistent and stable scores that are free from error or variation after repeated measurements, under different circumstances, by different persons, or using different measurement versions [20]. Efforts to determine the reliability of the FertiQoL are mostly limited to assessments of internal
consistency because of the potential for low temporal stability of psychological states [20]. The cycle of hope and despair cycle experienced with each menstrual or treatment cycle failure makes test–retest reliability problematic [8, 20, 35]. However, while a previous review found no evidence supporting the stability of the FertiQoL over time [17], a recent study by Chan et al. [36] investigated decisional conflict, regret, anxiety, depression, and fertility quality of life in 151 women in Hong Kong notified of an unsuccessful IVF cycle (T_0). Participants completed the questionnaire again during their consultation 2–3 weeks later (T_1) and finally, three months later (T_2). Descriptive statistics suggested relative stability over time, with Core scores of 63.99 (T_0), 64.67 (T_1), and 63.96 (T_2), Treatment scores of 62.03 (T_0), 61.70 (T_1), and 60.80 (T_2), and overall FertiQoL scores of 63.34 (T_0), 63.77 (T_1), and 62.91 (T_2). While the FertiQoL shows potential adequate test–retest reliability, additional studies are needed to support the currently limited findings.

**Internal Consistency**

Internal consistency, a measurement of reliability related to the homogeneity of items on a scale or subscale [20], has been extensively documented in multiple studies and compiled by the original authors on the Fertility Quality of Life website [24], as well as by Koert et al. [37] in a recent systematic review that summarizes the updated psychometric properties of the FertiQoL. Internal consistency has been reported using Cronbach’s alpha coefficients in all studies using FertiQoL. Internal consistency was tested during the generation of the FertiQoL [15, 33] and subsequently in multiple countries to determine the reliability of different translations and use of the measure with
individuals of multiple ethnicities and cultures. Internal consistencies were available for populations with infertility in the U.S., Canada, China, Denmark, Italy, Germany, Hong Kong, Hungary, Iran, Japan, Jordan, Korea, Netherlands, Poland, Portugal, Switzerland, Taiwan, and Turkey. See Tables 2 and 3 for updated internal consistencies with a description of the population sample and country of origin.

Previous studies indicated that FertiQoL is generally reliable in diverse populations of men and women with infertility. Internal consistency alpha scores range from 0.43–0.92 for the four subscales included in the Core (Emotional, Mind/Body, Social, and Relational) and 0.78–0.92 for the Core total (combined core subscales). While only some studies reported internal consistency for the optional Treatment module, those indicated moderate reliability with scores ranging from 0.67–0.84 for the Environment subscale, 0.64–0.79 for the Tolerability subscale, and 0.69–0.91 for the overall Treatment total. The internal consistency for the complete FertiQoL total ranges from 0.78–0.94.

While no specific rules exist defining satisfactory internal consistency, many agree that an alpha greater than 0.70–0.75 is generally considered acceptable [20, 80].

Overall, the four subscales that make up the core score of the FertiQoL showed moderate to high reliability. The Emotional (Cronbach’s $\alpha=0.71–0.90$) and Mind–Body (Cronbach’s $\alpha=0.78–0.89$) subscales showed high reliability with all alpha coefficients greater than 0.70. Aside from one study reporting low reliability ($\alpha=0.43$) in women with infertility from the U.S. and Canada trying to conceive between 12 and 48 months without medical intervention [40], the Social subscale (Cronbach’s $\alpha=0.61–0.84$; 4/19 studies $\alpha<0.70$) showed moderate reliability. Additionally, the Relational subscale has shown slightly lower reliability in several studies, with alphas ranging from 0.60 to 0.80.
(9/19 studies $\alpha$=0.60–0.68). Furthermore, two studies reported lower reliability of the Relational subscale with men. Donarelli et al. [34] described lower reliability of the Relational subscale in Italian men (0.61 vs. women: 0.68), and Sexty, Griesinger [46] corroborated these results with lower reliability in German men (0.65 vs. women: 0.70), suggesting the need to use caution when interpreting FertiQoL results for this subscale, particularly with men. Despite the slightly lower reliability in the Relational subscale, the internal consistencies reported indicate that the majority of the FertiQoL has demonstrated acceptable reliability, suggesting that the subscale items reliably measure the same underlying latent trait.
### Table 2
Internal Consistency Reported by FertiQoL Studies with Subscales

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample</th>
<th>Emotional</th>
<th>Mind-Body</th>
<th>Relational</th>
<th>Social</th>
<th>Core</th>
<th>Environment</th>
<th>Tolerability</th>
<th>Treatment Total</th>
<th>Scale Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aarts, van Empe [33]</td>
<td>472 women with infertility in the Netherlands receiving medical assistance for reproduction</td>
<td>.84</td>
<td>.85</td>
<td>.72</td>
<td>.74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asazawa, Jitsuzuki [38]</td>
<td>321 men undergoing IVF in Japan</td>
<td>.79</td>
<td>.82</td>
<td>.62</td>
<td>.67</td>
<td>.75</td>
<td>.65</td>
<td></td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>Asazawa and Mori [39]</td>
<td>233 couples (N=466) attending infertility clinics in Japan</td>
<td>.87</td>
<td>.88</td>
<td>.66</td>
<td>.75</td>
<td>.80</td>
<td>.79</td>
<td></td>
<td></td>
<td>93</td>
</tr>
<tr>
<td>Balsom and Gordon [40]</td>
<td>230 women in the U.S. and Canada trying to conceive 12-48 months without medical intervention</td>
<td>.71</td>
<td>.85</td>
<td>.68</td>
<td>.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boivin, Taliferman [15]</td>
<td>1305 women, 109 men with fertility difficulties in Australia, Canada, New Zealand, UK, USA</td>
<td>.90</td>
<td>.84</td>
<td>.80</td>
<td>.75</td>
<td>.92</td>
<td>.84</td>
<td>.72</td>
<td>.81</td>
<td>92</td>
</tr>
<tr>
<td>Donarelli, Lo Coco [34]</td>
<td>301 women, 286 men undergoing ART with primary infertility in Italy</td>
<td>.83</td>
<td>.83</td>
<td>.65</td>
<td>(F=.69)</td>
<td>(M=.61)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dural, Yasa [32]</td>
<td>389 women undergoing fertility treatments in Turkey</td>
<td>.82</td>
<td>.81</td>
<td>.73</td>
<td>.70</td>
<td>.89</td>
<td></td>
<td></td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>Hekmatzadeh, Bazarganipour [27]</td>
<td>300 women with infertility in Iran</td>
<td>.77</td>
<td>.78</td>
<td>.79</td>
<td>.77</td>
<td>.83</td>
<td>.79</td>
<td></td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>Kahyaoglu Sut H &amp; Balkanli Kaplan P [31]</td>
<td>89 women with infertility in Turkey</td>
<td>.74</td>
<td>.81</td>
<td>.68</td>
<td>.77</td>
<td>.90</td>
<td>.69</td>
<td>.71</td>
<td>.71</td>
<td>91</td>
</tr>
<tr>
<td>Masoulezadeh, Ghaheri [30] and Maroufzadeh, Ghaheri [41]</td>
<td>155 women with infertility in Iran</td>
<td>.82</td>
<td>.82</td>
<td>.64</td>
<td>.750</td>
<td>.91</td>
<td>.67</td>
<td>.64</td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>Ngai and Loke [42]</td>
<td>135 couples (N=270) with infertility in China</td>
<td>.79</td>
<td>.85</td>
<td>.60</td>
<td>.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>Pedro, Frederiksen [43]</td>
<td>161 women and 132 men enrolled for IVF or ICSI in 3 Danish clinics</td>
<td>.90</td>
<td>.84</td>
<td>.80</td>
<td>.75</td>
<td></td>
<td></td>
<td>.84</td>
<td>.72</td>
<td>92</td>
</tr>
<tr>
<td>Pedro, Canavaro [44]</td>
<td>265 women and 83 men undergoing evaluation or treatment for infertility in Portuguese clinics</td>
<td>.88</td>
<td>.89</td>
<td>.72</td>
<td>.78</td>
<td></td>
<td></td>
<td>.81</td>
<td>.75</td>
<td></td>
</tr>
<tr>
<td>Sextly, Hamadineh [45]</td>
<td>144 German, 126 Hungarian, 126 Jordanian new fertility patients and partners</td>
<td>Jordan</td>
<td>Jordan</td>
<td>Jordan</td>
<td>Jordan</td>
<td></td>
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<tr>
<td>Sextly, Griesinger [46]</td>
<td>362 women and 234 men attending a German infertility clinic</td>
<td>F=.83</td>
<td>M=.84</td>
<td>F=.70</td>
<td>F=.68</td>
<td>M=.67</td>
<td>M=.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Sample</td>
<td>Emotional</td>
<td>Mind–Body</td>
<td>Relational</td>
<td>Social</td>
<td>Core</td>
<td>Environment</td>
<td>Tolerability</td>
<td>Treatment Total</td>
<td>Scale Total</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Swift, Reis [47]</td>
<td>230 women undergoing infertility treatments in the US</td>
<td>.83</td>
<td>.90</td>
<td>.82</td>
<td>.71</td>
<td>.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szigeti, Grevenstein [48]</td>
<td>320 Hungarian women with infertility</td>
<td>.84</td>
<td>.87</td>
<td>.77</td>
<td>.73</td>
<td>.90</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volpini, Mazza [49]</td>
<td>323 women with fertility problem: in Italy</td>
<td>.87</td>
<td>.85</td>
<td>.70</td>
<td>.72</td>
<td>.90</td>
<td>.81</td>
<td>.71</td>
<td>.91</td>
<td>.78</td>
</tr>
<tr>
<td>Wardhol-Biedermann [50]</td>
<td>250 men seeking first-time fertility evaluation in Poland</td>
<td>.88</td>
<td>.89</td>
<td>.83</td>
<td>.84</td>
<td>.86</td>
<td></td>
<td></td>
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</tr>
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</table>

### Table 3
Reported Internal Consistency Subscale Ranges and Overall Totals

<table>
<thead>
<tr>
<th>FertiQol, Internal Consistency: Subscales Only</th>
<th>Subscalas and Ranges</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors</strong></td>
<td><strong>Subscale and Ranges</strong></td>
<td><strong>Sample</strong></td>
</tr>
<tr>
<td>Amini, Bazzazd [51]</td>
<td>Emotional, mind-body, and relational subscales range from F = .73-.86 and M = .69-.85</td>
<td>185 couples (N=370) with infertility seeking ART services in Canada</td>
</tr>
<tr>
<td>Andrei, Salvator [52]</td>
<td>Subscales range from .83 — .86</td>
<td>133 men and women with anatomical and non-anatomical infertility in Italy</td>
</tr>
<tr>
<td>Chen, Lau [36]</td>
<td>Subscales range from .76 — .93</td>
<td>151 women with infertility who did not get pregnant following IVF in Hong Kong</td>
</tr>
<tr>
<td>Ganeiro, Canavaro [53]</td>
<td>Relational subscale = .70</td>
<td>322 women, 111 men with infertility in Portugal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FertiQol, Internal Consistency: Totals and Subscales</th>
<th>Subscalas</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors</strong></td>
<td><strong>Subscale and Ranges</strong></td>
<td><strong>Sample</strong></td>
</tr>
<tr>
<td>Cheng, Stevenson [54]</td>
<td>Core Total = .91</td>
<td>126 women seeking infertility treatment in Taiwan</td>
</tr>
<tr>
<td>Csekepes, Bugán [55]</td>
<td>Total and subscales range from .63 — .88</td>
<td>270 couples (N=540) attending their first fertility consultation in Germany and Hungary</td>
</tr>
<tr>
<td>Domar, Gross [36]</td>
<td>Total and subscales range from .75 — .93</td>
<td>166 women undergoing their first homologous IVF cycle at a Boston-based U.S. infertility clinic</td>
</tr>
<tr>
<td>Li, Long [57]</td>
<td>Subscales range from .73 — .92 (experimental) and .70 and .90 (Control)</td>
<td>108 women attending a fertility clinic in China for their first IVF treatment</td>
</tr>
<tr>
<td>Li, Luo [58]</td>
<td>Subscales range from .74 — .86</td>
<td>253 women with infertility attending a fertility center in China</td>
</tr>
<tr>
<td>Li, Jie [59]</td>
<td>Subscales range from .78 — .85</td>
<td>262 women with PFL in China</td>
</tr>
<tr>
<td>Renzi, Di Turi [60]</td>
<td>Subscales range from .70 — .92</td>
<td>93 childless women in Rome undergoing ART (IVF/ET, or ICSI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FertiQol, Internal Consistency: Overall Tool Total</th>
<th>FertiQol Total</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Authors</strong></td>
<td><strong>FertiQol Total</strong></td>
<td><strong>Sample</strong></td>
</tr>
<tr>
<td>Kayabali and Yaman Sozbi [61]</td>
<td>.94</td>
<td>120 women in Turkey with primary infertility pregnant through ART in 2nd or 3rd trimester</td>
</tr>
<tr>
<td>Kim, Shin [62]</td>
<td>.93</td>
<td>121 couples with infertility with one or more infertility treatments in South Korea</td>
</tr>
<tr>
<td>Li, Zhang [63]</td>
<td>.93</td>
<td>498 women with infertility in China undergoing IVF-ET</td>
</tr>
<tr>
<td>Shin, Lee [64]</td>
<td>.93</td>
<td>186 women with primary infertility receiving infertility treatment at least once in Korea</td>
</tr>
<tr>
<td>Steuber and High [65]</td>
<td>.93</td>
<td>301 women with infertility in the U.S</td>
</tr>
<tr>
<td>Atanami, Aba [66]</td>
<td>.92</td>
<td>797 women receiving infertility treatment in Turkey</td>
</tr>
<tr>
<td>Kim, Hong [67]</td>
<td>.92</td>
<td>169 women undergoing IVF in Korea</td>
</tr>
<tr>
<td>Ni, Tong [68]</td>
<td>.92</td>
<td>137 women with repeated implantation failure in China</td>
</tr>
<tr>
<td>Camibol and Hikoz Cevik [69]</td>
<td>.91</td>
<td>125 women receiving infertility treatment in Turkey</td>
</tr>
<tr>
<td>Donarelli, Salerno [70]</td>
<td>.91</td>
<td>34 counseled and 34 matched non-counseled couples with primary infertility starting their first IVF, IF, or ICSI in Italy measured before beginning the cycle (T1) and on day of ET (T2)</td>
</tr>
<tr>
<td>Jing, Gu [71]</td>
<td>.91</td>
<td>768 women with infertility undergoing IVF-ET in China</td>
</tr>
<tr>
<td>Jing, Gu [72]</td>
<td>.91</td>
<td>588 women with infertility undergoing IVF in China</td>
</tr>
<tr>
<td>Maroufzadeh, Hosseini [73]</td>
<td>.91</td>
<td>180 couples with infertility in Iran</td>
</tr>
<tr>
<td>Kayaoglu Sut and Balkanli Kaplan [81]</td>
<td>.91</td>
<td>89 women with infertility in Turkey</td>
</tr>
<tr>
<td>Haemmerli Keller, Alder [74]</td>
<td>.89</td>
<td>109 women with infertility undergoing NC/IVF and dIF in Switzerland</td>
</tr>
<tr>
<td>Ha and Ban [75]</td>
<td>.88</td>
<td>150 couples with infertility in South Korea</td>
</tr>
<tr>
<td>Du and Dong [76]</td>
<td>.86</td>
<td>168 couples with infertility (N= 336), no children, and more than one ART cycle in China</td>
</tr>
<tr>
<td>Yousefzade, Resaie Alasian [77]</td>
<td>.86</td>
<td>180 men and women with infertility in Iran</td>
</tr>
<tr>
<td>Balcomb and Gordon [78]</td>
<td>.82</td>
<td>58 women with infertility between 12 and 48 months in the U.S. and Canada</td>
</tr>
<tr>
<td>Pozza, Dettore [79]</td>
<td>.81</td>
<td>226 individuals undergoing homologous and heterologous ART in Italy</td>
</tr>
</tbody>
</table>

Implications for Practice

Currently, the FertiQoL scores are open to interpretation by the individual administering the instrument or those taking the assessment online. Although a previous review found no evidence of test–retest reliability and a lack of clinically important cutoff scores [17], recent studies have suggested that core FertiQoL scores may correspond to clinically significant thresholds, including anxiety (< 55 to 59) and depression (< 51 to 52) in Dutch and Turkish individuals [31, 32], and marital dysfunction (< 74) in Italian men and women with infertility [34]. Healthcare providers, including physicians, physician assistants, nurses, nurse practitioners, and medical trainees (medical students, undergraduate and graduate nursing students), should be educated on the potential impact that infertility can have on an individual’s quality of life. While it was not specifically designed to detect pathological states of anxiety or depression, it can be used to identify individuals experiencing a more severe impact of infertility on their quality of life [15]. Applying this knowledge to clinical practice would expedite identification of those needing further assessment and additional specialty care when warranted. However, while there is some evidence to propose the translation of FertiQoL values to indicate clinically significant anxiety or depression, additional studies are needed to confirm the findings and ranges before implementation in everyday clinical practice.
Discussion

Findings from this review suggest that among the few available instruments measuring infertility-stress and fertility-related quality of life, the FertiQoL remains the most widely used fertility-specific quality of life measurement with adequate reliability and validity. Extensive feedback from individuals with infertility and reproductive professionals was integrated into the development of this fertility-specific quality-of-life tool [15]. Numerous studies have evaluated the reliability of the FertiQoL in populations of both men and women with infertility from different ethnicities, cultures, and causes of infertility, and except for the Relational subscale, it shows consistently high reliability in the core total, overall total, and remaining subscales. However, given the potential of psychological states to influence test scores, there is no established optimal time to administer the FertiQoL. Defining an appropriate time frame could be done by assessing test–retest reliability. Unfortunately, the cyclical nature of the hope and despair that individuals with infertility experience after each passing cycle can make test–retest analyses difficult [8, 20, 35], with only one study providing sound evidence of stability over time thus far [36]. Additionally, while the FertiQoL provides the most accurate quantitative measurement of the impact of infertility on an individual’s quality of life, it still cannot capture the small nuances of the lived experience of infertility that can only be elucidated using qualitative methodology.

Future research to further improve the FertiQoL should focus on two main concepts: 1) Evaluating its test–retest reliability and 2) Determining clinically significant threshold scores. Test–retest reliability could be evaluated by assessing several groups of individuals with infertility at multiple points throughout a cycle (e.g., person one tested
on day three, person two on day six, person three on day nine) and retesting at regular intervals (1–2 weeks or 1 month) or at the same time during the following cycle (e.g., person one at day three again). While failure or success in achieving a pregnancy, either through assisted reproductive technology or naturally, may affect the results of the analysis, this would also be beneficial to understand how these pivotal events can impact the quality of life for those with infertility. This could also provide insight into FertiQoL’s ability to detect change or capture a participant’s true score [20].

While several instruments exist to measure generic quality of life, depression, and anxiety, an infertility-specific measurement allows clinicians and researchers to differentiate the impact of infertility versus general stressors on an individual’s quality of life [15]. The subscales of the FertiQoL provide a more precise determination of problematic areas that can lead to an impaired quality of life, like relational or emotional concerns. Clinicians can use the FertiQoL to identify areas in need of intervention and offer additional support or resources when possible. The FertiQoL can also provide an opportunity to reinforce an open line of communication between clinicians and patients. Individuals who utilize avoidance coping or conceal negative emotions about infertility are more likely to experience feelings of stigma and depression that negatively affect quality of life [67, 71]. An active approach to monitoring patients for infertility-related quality of life conveys a supportive environment where clinicians are open to communication, providing psychosocial resources, and introducing strategies to improve coping mechanisms and communication within an identified support system.
**Strengths and Limitations**

Extensive efforts were made to include all literature that used the FertiQoL tool and reported psychometric properties. Although no time limit was placed on the search parameters, additional literature may have been missed due to the selection of keywords, chosen databases, and limitations to studies published in English. Additionally, most of the studies included populations with infertility seeking treatment, excluding a critical portion of individuals who chose not to or could not afford to pursue infertility treatment. Despite the limitations outlined, this report offers several strengths. This is the most recent comprehensive literature review and synthesis of a psychometric evaluation of the FertiQoL. A systematic approach was used to identify studies available in English that reported FertiQoL psychometric properties from three comprehensive databases: PsycINFO, PubMed, and CINAHL. It outlined its implications for use and identified areas in need of further investigation to advance current research on infertility-related quality of life.

**Conclusion**

This review demonstrates that the FertiQoL is a sound measurement tool with adequate reliability and validity for use with individuals with infertility from various ethnicities and cultures. With further investigation into clinically significant thresholds, the FertiQoL could be used to reduce patient burden as a single, initial assessment tool in individuals experiencing fertility challenges to identify those needing further assessment and care. Despite the ability of the FertiQoL to ascertain potential areas of infertility-related challenges, like mental health and relational problems, the use of qualitative
research methodologies should be considered to fully explore the multifaceted issues faced by people with infertility and identify the best ways to deliver comprehensive clinical care to meet their needs.
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CHAPTER 4

A PHENOMENOLOGICAL EXPLORATION OF THE MENTAL HEALTH EXPERIENCES OF YOUNG WOMEN WITH DIMINISHED OVARIAN RESERVE

by

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Infertility is a reproductive disease that renders an individual unable to conceive and affects one in six individuals. One cause of infertility is diminished ovarian reserve (DOR), which reduces the quantity and/or quality of a female's oocyte pool. Although typically indicating normal ovarian aging during the late 30s and early 40s, DOR can also impact younger women, increasing their risk for psychological distress from an unexpected diagnosis. A phenomenological approach examined the mental health experiences and perceptions of infertility-related mental health care of young women with DOR. Women diagnosed with DOR by age 35 in the United States who experienced emotional distress during infertility were recruited from infertility-specific social media and via snowball sampling. Participants completed a demographic survey and semi-structured individual interview that was audio-recorded, transcribed verbatim, and analyzed using a phenomenological approach. Ten women ages 27-41 completed the study. On average, participants were 30 years of age at the time of DOR diagnosis (age range 25-35), primarily Caucasian (90%), and married (90%). Two main themes were found: 1) Young women with DOR feel like a “forgotten community” coping with an invisible disease; and 2) Not all fertility clinics are created equal. Participants perceived their diagnosis as devastating and hopeless and urged others to find a provider with ample experience treating patients with DOR. This study helped to understand how young women with DOR perceive their mental health and identified a significant need for
advancing towards more holistic infertility health care that encompasses both physical and mental health.

**Keywords:** Infertility, diminished ovarian reserve, mental health, phenomenology, qualitative

**Patient or Public Contribution**

As part of a member check, two participants provided feedback during the analysis and confirmed that the findings were congruent with what was conveyed.
A PHENOMENOLOGICAL EXPLORATION OF THE MENTAL HEALTH EXPERIENCES OF YOUNG WOMEN WITH DIMINISHED OVARIAN RESERVE

One in six individuals worldwide experience infertility in their lifetime (Geneva: World Health Organization, 2023). Infertility, a reproductive disease defined by the inability to conceive after 12 months of unprotected sexual intercourse (Practice Committee of the American Society for Reproductive Medicine [ASRM], 2013; World Health Organization, 2022), can be female or male-specific, unknown, or a combination of factors. Infertility includes etiologies like abnormal sperm quantity or morphology, uterine abnormalities, ovulatory dysfunction, endocrine disorders, or diminished ovarian reserve (DOR; Penzias et al., 2021).

Ovarian reserve testing assesses the quantity of a woman’s oocyte pool and reflects reproductive potential (Gleicher et al., 2011). A decline in ovarian function usually begins during the mid-30s, but can occur in the 20s and early 30s (Pastore et al., 2017). Women with DOR typically experience regular menstrual cycles, rarely exhibiting outward symptoms other than the inability to conceive (Nikolaou & Templeton, 2004; Rasool & Shah, 2017). Most patients are diagnosed with DOR by a reproductive specialist in conjunction with treatments like assisted reproductive technology (ART; The Practice Committee of the American Society for Reproductive Medicine, 2012; Tremellen & Savulescu, 2014). In 2019, 298,689 cycles of ART were reported to the Society for Assisted Reproductive Technologies (SART; 2019). Of these cycles, 39,450
(13%) were diagnosed with DOR, and 3,264 (8% with DOR; 1% of the total cycles) were age 40 or younger.

Involuntary childlessness creates significant emotional turmoil (Galst, 2018). Many patients desire mental health support but report a lack of resources from their reproductive providers (Gelgoot et al., 2020; Hoff et al., 2018; Salakos et al., 2004). Women with infertility report anxiety and depression symptoms 25-60% of the time (Domar et al., 1992; Rooney & Domar, 2018). These high rates suggest significant gaps exist in addressing infertility mental health needs (Aarts et al., 2012; Cousineau & Domar, 2007; Gameiro et al., 2013). Infertility-related stress can also impact physical, mental, and financial health and quality of life, contributing to poor psychological outcomes if left unaddressed (Rostad et al., 2014). Limited insurance coverage for infertility treatments burdens patients with substantial out-of-pocket costs and no guarantee of success, potentially limits reproductive options for those unable to afford care, and further compounds infertility-related stress (RESOLVE: The National Infertility Association, n.d.; Schneider & Forthofer, 2005).

Evidence suggests that women with DOR experience poorer psychological health (Nicoloro-SantaBarbara et al., 2017), and younger women may have different mental health experiences from the increased psychological burden of an unexpected diagnosis (Nikolaou & Templeton, 2004; Rasool & Shah, 2017). Women diagnosed with DOR at an early age face additional risks of long-term effects beyond reproduction and immediate quality of life, including decreased bone mineral density, sexual distress, disturbed sleep, and a higher likelihood of premature ovarian insufficiency (Pal et al., 2010). Because DOR remains largely understudied, there is inadequate understanding of
how young women with DOR perceive their mental health. This study aims to describe
the lived experiences of infertility and mental health in young women diagnosed with
infertility caused by DOR in the U.S guided by two research questions: 1) How do
women diagnosed by age 35 with infertility caused by DOR describe their mental health
during infertility? and 2) How do women diagnosed by age 35 with infertility caused by
DOR perceive their mental health care?

Theoretical Framework

Infertility can cause immense stress for those desiring parenthood. We designed
an adaptation of the theory of stress and coping to clarify relationships between
infertility-specific moderators and adaptational outcomes, guide qualitative data
collection, examine psychological aspects of participants’ lived experiences, and explain
how individuals present different perceptions of infertility experiences. This theory
focuses on stress appraisal responses based on person-environment relationships (Lazarus
& Folkman, 1984; McEwen & Wills, 2019). Moderators affect stress appraisals and
generate emotion to influence coping, which mediates stress appraisals and emotional
responses (Folkman & Lazarus, 1988; Lazarus & Folkman, 1984). See Figure 1 for
theoretical framework.
Methods

A qualitative phenomenological design was used to elicit mental health experiences of young women with DOR. While numerous quantitative studies reveal that infertility causes emotional distress, they aim to control for human subjectivity, historical, and social influences that interject meaning into lived experiences (Giorgi, 1985). Conversely, qualitative methodology embraces individual perceptions (Giorgi, 1985).

Phenomenology permits deeper understanding of complex and poorly understood phenomenon shared by a group of individuals by allowing it to speak for itself through in-depth interviews without introducing preconceived ideas by the researcher (Creswell & Poth, 2018; Giorgi, 1985; Husserl, 1970; Moustakas, 1994). Participants reveal
intimate perspectives of their experiences in relation to their world, reported in themes and direct quotes, allowing researchers to view their subjective reality (Giorgi, 1985; Holloway & Galvin, 2017; Moustakas, 1994).

**Participants**

Consistent with a phenomenological approach (Moustakas, 1994), purposive sampling was used to recruit ten women diagnosed with DOR by age 35 that experienced psychological distress from infertility-specific social media, U.S.-based infertility clinics, and via snowball sampling (Creswell & Poth, 2018; Holloway & Galvin, 2017). Recruitment ceased once data saturation was met. The goal of phenomenology is to describe the phenomenon experienced by a smaller number of individuals, not necessarily to make findings generalizable (Creswell & Poth, 2018). Overly large samples are unnecessary because too many participants can result in data lacking richness and uniqueness that fails to capture the phenomenon’s essence (Holloway & Galvin, 2017). A sample size between five and 15 is adequate to obtain data saturation (Creswell & Poth, 2018; Dukes, 1984; Lincoln & Guba, 1985). Participants were excluded for current or previous cancers, severe mental health illness requiring hospitalization prior to infertility, current or previous suicidal ideation, or adnexal surgery prior to infertility. Chemotherapy, radiation, and gynecological or ovarian surgical procedures can cause iatrogenic infertility and are known causes of DOR, with most women aware of the potential diagnosis (Bath et al., 1999; Georgescu et al., 2008; Rasool & Shah, 2017). Because the goal was to explore mental health of women who may not expect the
diagnosis, patients with iatrogenic infertility were excluded. See Table 1 for inclusion and exclusion criteria.

Table 1
*Diminished Ovarian Reserve Inclusion and Exclusion Criteria*

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Female biological sex</td>
<td>1. Previous or current diagnosis of cancer</td>
</tr>
<tr>
<td>2. Diagnosis of infertility caused by unexplained DOR by age 35</td>
<td>2. History of surgical procedures on ovaries, pelvic area, or uterus before infertility</td>
</tr>
<tr>
<td>3. Self-reported experience of anxiety or depression during infertility</td>
<td>3. History of severe mental health illness requiring hospitalization prior to infertility</td>
</tr>
<tr>
<td>4. Ability to read and understand English</td>
<td>4. Current or previous suicidal ideation</td>
</tr>
<tr>
<td>5. Have a working telephone number, email address, and internet connection</td>
<td></td>
</tr>
<tr>
<td>6. Reside in the United States</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* DOR, diminished ovarian reserve.

Potential participants were given a study flyer and information sheet containing the purpose, risks, benefits, compensation, and principal investigator’s (PI) contact information. Contact information for counselors and support groups was also provided (Holloway & Galvin, 2017). Eligibility criteria were reviewed with women who were given a chance to ask questions before informed consent was obtained. Institutional review board approval was established prior to study initiation, and participants received $30 compensation.
Data Collection and Analysis

If eligible, participants were invited to complete a confidential sociodemographic survey using an online survey collection tool, Qualtrics (www.qualtrics.com), and a one-on-one audiovisual interview.

Survey

The survey collected demographics, infertility history, and mental health experiences. Items were selected based on associations from previous studies between age, education, length of relationship, and infertility history with depression and anxiety (Li et al., 2021; Maroufizadeh et al., 2018; Omani-Samani et al., 2018), and were vetted by the PI’s dissertation committee, comprised of experts in women’s health, infertility, psychology, and research methodology. Descriptive statistics were used to describe participant demographics using IBM SPSS Statistics © (Version 28.0.1.1). Results are reported using mean (SD) or frequency (%).

Interview

Participants completed semi-structured audiovisual interviews lasting 60-90 minutes conducted by the PI, a doctoral candidate at a School of Nursing in the southeastern U.S. Interviews began with broad questions: “Tell me about your infertility journey and where you are with it as of now” and “How would you describe your mental health during infertility?” (Creswell & Poth, 2018; Moustakas, 1994). Prompts were used to explore experiences by having participants provide examples or descriptions. Field
notes were collected during and immediately after interviews to reflect on significant events or thoughts while they were clearly remembered (Holloway & Galvin, 2017).

Interviews were audio-recorded, transcribed verbatim, and uploaded into NVivo (Version 12.7.0), a computer-assisted qualitative data analysis software, to assist in the management of data and simplify the coding process (Merriam & Tisdell, 2016). Transcripts were analyzed concurrently with data collection using Colaizzi’s (1978) phenomenological method. Transcripts were read several times to gain an overall sense of what participants were trying to convey (Colaizzi, 1978; Creswell & Poth, 2018). Significant statements were extracted and meanings relevant to mental health and health care were aggregated into themes similar across the interviews, while returning to the transcripts to ensure validation or noting discrepancies (Holloway & Galvin, 2017). Theme descriptions were compiled into an exhaustive description of the phenomenon and an essential structure of the experience was identified (Holloway & Galvin, 2017). Epoche, bracketing personal experiences and perceptions, was performed prior to and throughout data analysis using field notes to record emerging ideas, personal reflections, and potential biases (Merriam & Tisdell, 2016). Member checking with two participants was used to avoid misinterpretation, confirm an accurate reality was presented, and establish credibility (Holloway & Galvin, 2017). Ample time was spent with the data and participants to ensure data saturation (Merriam & Tisdell, 2016). Rich descriptions of participant data and quotes allows researchers to determine transferability of results (Holloway & Galvin, 2017; Lincoln & Guba, 1985). See Table 2 for a comprehensive list of strategies to achieve trustworthiness.
Table 2
Strategies to Achieve Trustworthiness

<table>
<thead>
<tr>
<th>Qualitative terms to assess trustworthiness</th>
<th>Strategies to achieve trustworthiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Credibility</td>
<td>Member-checking of interpretation of findings, spending adequate time with participants and data</td>
</tr>
<tr>
<td>Transferability</td>
<td>Using thick, rich descriptions of study setting, participant characteristics, and participant quotes</td>
</tr>
<tr>
<td>Confirmability</td>
<td>Using reflexivity (epoche), peer review (dissertation committee), audit trail of data management and analysis</td>
</tr>
</tbody>
</table>

Note. (Creswell & Poth, 2018; Holloway & Galvin, 2017; Lincoln & Guba, 1985; Merriam & Tisdell, 2016; Terrell, 2016)

Results

Ten women ages 27 to 41 (average age 33.6) residing in the Midwest, South, and Northeastern regions of the U.S. participated in the study. The majority were white (90%), married (90%), working full-time (70%), and had obtained either professional or graduate degrees (70%). The average age of DOR diagnosis was 30, with a range of 25 to 35 years old. Most women (80%) experienced both anxiety and depression during infertility, yet only four out of ten participants (40%) were offered any mental health resources by their health care provider. See Tables 3 and 4 for additional participant demographics and an overview of each woman’s infertility journey.
### Table 3

**Participant Demographics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N = 10</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>Current age (range 27-41)</td>
<td>33.6</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Age at DOR diagnosis (range 25-35)</td>
<td>30.5</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Relationship status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>9</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Racial/ethnic background</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>9</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Two or more races</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/Caucasian &amp; Black/African American</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Highest level of education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>College Degree</td>
<td>3</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Professional or Graduate Degree</td>
<td>7</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>Current work/school status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working full-time</td>
<td>6</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Working full-time/taking educational courses at home</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Working part-time</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Stay-at-home parent</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Attending school full-time</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Current physical status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>2</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>3</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>4</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Current mental status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>3</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>4</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>3</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Currently have children or are pregnant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes, using assisted reproduction</td>
<td>7</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Number of miscarriages prior to live birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>4</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>5 or more</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Assisted reproductive treatments used by participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications to encourage ovulation (Clomid)</td>
<td>7</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>IUI</td>
<td>6</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>IVF or ICSI</td>
<td>9</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Egg donation</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Sperm donation</td>
<td>1</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

*Note: IUI, intrauterine insemination; IVF, in-vitro fertilization; ICSI, intracytoplasmic sperm injection.*
### Table 4
Overview of Participant Journey of Infertility and Treatment

<table>
<thead>
<tr>
<th>Current age (Age at DOR)</th>
<th>Journey Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>27 (26)</strong></td>
<td>Tried for 2 months, miscarried at 4 weeks, tried another 6 months, sought FS and diagnosed with DOR, Clomid X 1, IUI x 3, IVF x 1 retrieved 7 eggs, 5 embryos, and one successful transfer resulting in pregnancy and live birth.</td>
</tr>
<tr>
<td><strong>36 (35)</strong></td>
<td>Ovarian testing at age 35 due to single relationship status to determine time to consider reproductive options, OB diagnosed severe DOR, tried for 8 months, IUI X 5 (No IVF coverage), advanced from DOR to POI, will need donor eggs &amp; sperm or embryos to proceed.</td>
</tr>
<tr>
<td><strong>34 (29)</strong></td>
<td>No contraception for 2 years, actively tried another 6 months, PCP suggested 6 more months, PCP drew labs and referred out to FS who diagnosed DOR/male factor, IVF X 1 resulted in 2 embryos, 1\textsuperscript{st} fresh transfer was successful and resulted in pregnancy and live birth, sibling transfer was unsuccessful, unsure about pursuing another IVF cycle.</td>
</tr>
<tr>
<td><strong>38 (35)</strong></td>
<td>Tried for 1 year, sought FS who diagnosed DOR, IUI X 2 both resulted in pregnancy - 1 empty sack, 1 ectopic, 1\textsuperscript{st} round IVF resulted in 5 embryos (1 normal), 2\textsuperscript{nd} round no embryos, donor eggs were suggested, 1\textsuperscript{st} round with donor eggs resulted in 1 genetically normal embryo, transfer was unsuccessful, endometrial biopsy revealed need for extra day of estrogen support, 2\textsuperscript{nd} donor resulted in 3 embryos and 1\textsuperscript{st} transfer was successful with pregnancy and live birth.</td>
</tr>
<tr>
<td><strong>31 (30)</strong></td>
<td>Tried for 3 months, pregnancy ended in miscarriage, sought FS after 1 year and diagnosed with DOR, IVF X 1 converted to IUI, FS pushed donor eggs, sought 2\textsuperscript{nd} opinion and changed FS, IVF X 1 and transfer resulted in pregnancy - 16 weeks pregnant at time of interview.</td>
</tr>
<tr>
<td><strong>35 (30)</strong></td>
<td>No contraception for 2 years, actively tried another 6 months, OB/GYN told to keep trying, self-referred to FS and diagnosed with severe DOR, IUI x 3, started IVF but got delayed with COVID, resumed after removal of “elective” status, 1\textsuperscript{st} IVF round resulted in 11 eggs, no embryos, 2\textsuperscript{nd} round resulted in poor quality eggs and 2 failed embryo transfers, FS pushed donor eggs, transferred to new FS, IVF X 1 resulted in 3 normal embryos, 1\textsuperscript{st} transfer successful and resulted in pregnancy and live birth, spontaneous pregnancy at time of interview.</td>
</tr>
<tr>
<td><strong>41 (34)</strong></td>
<td>Tried for 1 year, sought FS and diagnosed with severe DOR, not a candidate for treatment at their clinic, went to several FS until one was willing to take as patient, IVF X 7 resulted in 3 embryos, 1\textsuperscript{st} transfer resulted in pregnancy and live singleton birth, 2\textsuperscript{nd} transfer was successful and resulted in identical twins, spontaneous pregnancy at age 40, now has 4 children.</td>
</tr>
<tr>
<td><strong>33 (31)</strong></td>
<td>Pregnant 6 months after trying, miscarried at 5 weeks, pregnant 5 months later, miscarried at 5 weeks, sought FS at 1 year, testing was normal, told to keep trying, changed jobs for insurance, tried for another year with 2 miscarriages, FS diagnosed mild DOR, tried another year, AMH decreased, IVF x 2, 1\textsuperscript{st} round resulted in 1 embryo, 2\textsuperscript{nd} round resulted in 6 embryos, 1\textsuperscript{st} embryo transfer resulted in chemical pregnancy, 2\textsuperscript{nd} transfer resulted in pregnancy and live birth.</td>
</tr>
<tr>
<td><strong>33 (30)</strong></td>
<td>Sought OB after 1 year of trying, referred to FS, IVF X 1 resulted in 8 eggs, 2 embryos, 1\textsuperscript{st} transfer failed, advocated for endometrial receptivity test and treated for uterine lining inflammation, 2\textsuperscript{nd} transfer successful and resulted in pregnancy and live birth.</td>
</tr>
<tr>
<td><strong>28 (25)</strong></td>
<td>Started experiencing perimenopausal symptoms at age 25, OB/GYN diagnosed with severe DOR, advised to freeze eggs, went to FS, IVF X 6 resulted in 3 embryos, medical history indicates need for surrogate when ready for embryo transfer.</td>
</tr>
</tbody>
</table>

*Note: FS, fertility specialist; OB/GYN, obstetrician/gynecologist; PCP, primary care physician; IUI, intrauterine insemination; IVF, in-vitro fertilization; POI, primary ovarian insufficiency*
**Theme 1: Young women with DOR feel like a “forgotten community” coping with an invisible disease.**

Women experienced shock, loneliness, stigma, anxiety, and depression after receiving a diagnosis of DOR. Coping mechanisms helped manage their mental health, but with so much out of their control, participants felt “out of sync” and often overlooked by friends, family, and health care providers.

**Subtheme: A devastating diagnosis: your body is failing you.**

Participants explained that being diagnosed with DOR at a young age was unexpected, causing significant distress from the perpetual unknown, feeling like their body was failing, potentially needing donor eggs, and a constant feeling of “running out of time”. Several participants had never heard of DOR or assumed it only affected older women. However, many had already begun experiencing perimenopausal symptoms that negatively affected their anxiety and quality of life: “I had never even heard about that [DOR]. And then you've realized that there's this whole underground community of women that are like me, that are young and that are perimenopausal for some unknown reason that nobody is talking about or investigating,” (Participant 9). With multiple miscarriages, unanticipated poor fertility treatment outcomes, and the relentless need for self-advocacy, participants portrayed DOR as “a hopeless diagnosis.” Participant 6 explained, “I think DOR is the most devastating infertility diagnosis you can get, because out of all the diagnoses, it's the only one that's immediately accompanied with the egg donor conversation.” Frustrated and feeling like their body had failed them, most participants believed that needing donor eggs was another setback to their psyche and identity as a woman and mother. Many women feared they would never become mothers.
Participant 5 depicted the multifaceted and crucial decisions faced by women with DOR who often need aggressive treatment protocols to overcome reduced ovarian function: “Do you do IVF and spend all this money, and possibly not have a positive result? But again, it's like you're against the clock. So, if you're going to do IVF, it's kind of a ‘do-it-now’ sort of thing.”

**Subtheme: It’s all in your head: taking care of your mental health.**

DOR was detrimental to participants’ mental health. Participant 5 explained, “It was like processing a death to me. Most people do not understand this: it's life changing. You see your life going in one direction, and then you have to completely pivot.” Constant stretches of waiting and a lack of control contributed to the ever-present anxiety and depression seeping into their lives: waiting to seek diagnosis or treatment, waiting for retrieval or fertilization results, or waiting for their turn to become mothers. “I might never get the chance to be pregnant and carry a child, and I’ll never know that experience and I’ll leave this world not knowing that. And that scared me and it made me really sad and depressed,” (Participant 3). Even after achieving pregnancy, Participant 1 explained how anxiety continued to loom: “I just wasn't expecting 10 months of so much anxiety, of ‘surely I'm gonna lose this baby’. Of course I'm going to. I've worked so hard. Like why would something not sweep me off my feet?” Participants described intense loneliness and social isolation, further intensified by infertility-related stigma. Women increased physical activity, found strength through religion, utilized acupuncture and meditation, and set boundaries to distance themselves from social media and social events to circumvent situations deleterious to their mental health. Participant 8 explained,
“At a certain point in my infertility journey, I purposely did things to protect my own mental health.” Women with DOR found some friendships failed to withstand this period of isolation and difficulty: “I even lost like a best friend last year, pretty much over all of this. It's like people don't want to be around things that are uncomfortable.”

Approximately half of the women used traditional counseling and medications to manage their mental health. However, general counselors shared many misconceptions with the lay public. Women receiving care from general therapists had to explain every detail of their infertility and were often offered unsolicited or callous advice, minimizing their values and concerns, like asking why not consider adoption or foster care. Conversely, infertility-specific counselors delivered empathetic treatment understanding of alternative family structures, infertility stigma and isolation, perinatal and infant loss, peri- and post-partum anxiety and depression, and the cyclical emotions surrounding treatment cycles.

Participant 8 described positive experiences with an infertility-specific counselor:

She herself [counselor] had gone through IVF multiple times, which was a big reason that I wanted her as well. Because I'm sorry, but if you haven't been through it, you have no idea. She just helped with coping mechanisms on ways to think through things…it just honestly just felt good to talk to someone weekly who literally had gone through it.

Despite clear advantages of specialized counselors, many participants struggled to locate someone with infertility-specific knowledge in their area, noting they were almost “impossible to find.”

Subtheme: Unless you’ve been through it, you can’t understand.

Many women struggled to share experiences with friends, family, and coworkers, fearing their inability to understand or show empathy. Participant 3 described one reason
women often conceal their infertility, perpetuating the stigma and forced silence about infertility and mental health:

I didn't want to share about it. I felt like people wouldn't understand. And then, when I did share about it with some people, they asked lots of questions, and that got very overwhelming for me to answer all the questions of what led us to all of this.

Some participants realized that infertility stigma and misconceptions continued beyond personal relationships and into professional lives. One participant lost a job over the need to reduce work hours to juggle IVF and maintain her mental health. Although many women explained that friends and family wanted to provide support and encouragement, they simply did not know how to help. Some women distanced themselves, while others found the more they shared, the better they felt. One idea was echoed by most women: Unless you have been through infertility, you cannot understand. After failed treatments and wondering if she would ever have children, Participant 6 explained: “Infertility is hard. Doing IVF is harder, but no one talks about when IVF fails, and that's a really rare hell that only certain people know…That's when things just feel really impossible and scary and heavy and alone.” Many women sought answers and support through DOR-specific social media. Finding others with DOR experiences fostered belonging and minimized loneliness and isolation.

And you know all these women on Instagram and Facebook, whom I've never met in person, it's like some of them were my biggest cheerleaders on my darkestdays, and I'm forever grateful for that because I feel like, unless you've been through IVF and then failed IVF, it's like you have no idea what this is like.

Participants explained that connecting with others with DOR was one of the most helpful things. Whether it was through social media, counseling, or support groups hosted by clinics or organizations like RESOLVE: The National Infertility Association, talking
about their struggles helped destigmatize DOR while potentially helping others feel more open to sharing.

**Theme 2: Not all fertility clinics are created equal.**

Many participants realized early on that not all fertility clinics are created equal. There was a lack of provider transparency and education about DOR and a general absence of mental health resources offered after receiving a devastating diagnosis. With stark differences in treatment outcomes from one infertility clinic to another, many participants urged others to research and find health care providers specializing in DOR before beginning infertility treatments.

**Subtheme: Setting the expectation.**

Participants expressed general dissatisfaction with provider communication. While providers frequently offered minimal information about DOR, when it was discussed, medical jargon made it challenging to understand. More often, providers rushed over the diagnosis, failing to expound on how DOR relates to the big picture of their infertility. Women felt like DOR was often downplayed, resulting in inadequate preparation for the possibility of poor treatment outcomes. Participant 1 was shocked to learn that a low number of follicles was expected with DOR:

Nobody really explained to me exactly what that [DOR] looked like, and I didn't know until I went to my very last IVF ultrasound when they're, ‘Oh, we'll be lucky if we get one embryo out of those 7.’ So it wasn't really until that, that I understood… because a lot of my friends went through IVF. They all got like 20, 30 eggs, and I barely have 7.
Participants desired more transparency throughout their care. Setting clear expectations would better prepare women for uncertain outcomes and potential psychological repercussions:

So eventually, we did our first round of IVF, and we got 11 eggs, which I was shocked. And then 0 embryos, which I didn't even know that was a possibility…So that was kind of the beginning of the really hard and tough stuff of having DOR.

Women sought information online or from DOR-specific social media, but sadly realized that aside from social media narratives, they found minimal legitimate medical information applicable to young women with DOR. Instead, it was portrayed as affecting older women, generating additional anxiety, depression, and loneliness.

**Subtheme: Dismissing patient concerns: is this a case of medical gaslighting?**

Because DOR was less common and seemingly less understood, participants often found their concerns disregarded by health care providers. This led to realizations that reproductive success would require extensive self-advocacy. Despite recommended practices to seek infertility care after one year, many participants were told by obstetricians and reproductive specialists that they were young and to keep trying. After 2.5 years of trying to conceive, Participant 6 self-referred to a specialist after being dismissed by her obstetrician: “I saw my regular OB/GYN, who just totally dismissed me, and was like, ‘You're so young. You've got time. There's nothing to be worried about.’” Similarly, after multiple miscarriages and more than a year of trying, Participant 8’s first reproductive specialist advised her to keep trying, prompting her to search for a clinic willing to take her care more seriously. One woman sought advice from her obstetrician about ethical sperm donation to treat severe DOR without a partner. Rather
than taking her seriously, she felt her concerns were invalidated when her provider laughed and responded, “It sounds like you've been Googling too much. I wouldn't worry about it.”

Following diagnosis, many women were met with flippant recommendations to use donor eggs without regard to the seriousness of the conversation or the patient’s goals. Several women speculated whether the hasty recommendations were based on provider discomfort and lack of experience with DOR or a callous desire to protect clinic success rates. Whether or not these speculations are accurate, women perceived a lack of empathy or interest in goal-concordant care where providers failed to account for patient goals, usually due to a lack of communication. After several women were told by providers they would be unable to treat them without donor eggs, they sought care from other clinics with DOR experience and successfully conceived with their own eggs. Participant 7 was informed by several providers that her ovarian reserve was so poor she did not qualify for treatment. However, after finding a provider who was transparent about outcome expectations and prepared to help her achieve her goals, she was able to become a mother and now has four daughters: one singleton birth after a single embryo transfer, identical twins after a single embryo transfer, and one natural conception at the age of 40. She explained how it felt to move from being told ‘no’ over and over again to finding a provider willing to deliver person-centered care and support:

   I mean, if all the doctors that told me to go away knew the story! I just feel like the bottom line for me is don't treat women like that like…I truly felt like [in my last clinic] I had people with me during my journey, like at the clinic, that actually cared and spent time with me and were willing to hear how I wanted things to go.

In addition to being “pushed” to using donor eggs, many women reported constantly advocating for themselves. From self-referrals to a reproductive specialist, asking for
complementary treatments to improve cycle outcomes, or requesting egg retrievals with three or fewer follicles, women with DOR shared that the onus of their treatment plans was placed on them, rather than the provider, which increased their already high stress and anxiety levels. Participant 9 explained, “It was a little disappointing how much I had to advocate for me. And I don't want to say I didn't feel taken care of, but I definitely felt like nobody is going to care about your success as much as you are.” After speaking with other women who had unsuccessful embryo transfers, one participant advocated for an endometrial receptivity test before transferring her one remaining embryo. Her testing indicated uterine inflammation that was subsequently treated, resulting in a successful embryo transfer. However, had she not connected with others and advocated for testing, she may have never become a mother.

**Subtheme: A demand for holistic care.**

Participants made a universal plea for holistic infertility health care, beginning with improved provider communication, transparency, and education about diagnoses. Current communication was seen as lacking empathy or too medical without regarding the psychosocial aspects of DOR. Several women indicated that DOR was inadequately explained, leading to limited knowledge of potential impacts on their prognosis and seeking out information on their own. Participant 5 described a positive experience after switching to a provider who exemplified more holistic and transparent care: “At no point was there any sort of toxic positivity. It was never false hope, like this is going to work or this is going to be great. There was never any of that, but just the way that he handled a very difficult situation made all the difference for us,” versus the negative experience of
Participant 2: “There was no information given, just the diagnosis, and I don't think that’s satisfactory.” Similarly, many participants were left to seek information for themselves, usually through anecdotal accounts on social media, which may or may not be helpful: “I think there's so much misinformation online, and there are so many toxic support groups, and when you're not given anything official, you don’t know where to turn.”

Acknowledging the difficulty of the situation and conveying empathy, rather than a strict medicalization of infertility, was seen as an effective way to build patient trust and rapport. Unfortunately, many women, like Participant 7, experienced poorly handled situations:

Someone over the phone is basically telling me that I’ll never have children. How do you pick up the phone and call somebody like that? That's a conversation you have in person. You're basically telling a woman who wants nothing more than to be a mother over the phone that they're not gonna have kids.

Participants recommended that mental health resources be included as a standard of care. Suggestions included providing access to infertility-specific counseling, peer support groups, or peer-to-peer support. Participant 6 justified the need for counseling, explaining, “It’s a devastating diagnosis that you get, that you’re probably not prepared for, that has a possibility of changing your entire life. Why wouldn’t you have counseling services for that?” While access to infertility-specific counseling was one of the most requested items, a simple acknowledgment and initial discussion about potential emotional distress goes a long way in reducing anxiety and depression:

Even having that conversation on the front end is really just demonstrating that they know that it's a very stressful time. If you do experience anxiety or depression, it almost gives you permission, like it validates any feelings that you would have throughout the process. (Participant 9)
Discussion

This study found that young women perceive DOR as a devastating diagnosis surrounded by stigma that gives rise to emotional distress and loneliness. Participants revealed ample opportunities for improvement in infertility-specific medical and mental health care: being transparent about treatment expectations, acknowledging the difficulty of the situation, and providing mental health resources. Results suggest that young women with DOR have similar mental health experiences as others with infertility, like isolation (McCarthy, 2008), anxiety and depression (Massarotti et al., 2019), and social stigma (Whiteford & Gonzalez, 1995). However, several traits are distinct to DOR: poorer treatment results, feeling like the body and ovaries are failing, running out of time, and a recommendation to use donor eggs.

While the term ‘medical gaslighting’ seems extreme, it denotes situations where health care providers dismiss patient concerns or symptom accounts they deem normal or manifestations of stress (Barnes, 2023). Women and minorities experience more incidences of medical gaslighting and are more likely to be dismissed or misdiagnosed when presenting with myocardial infarctions (Wu et al., 2018) or poorly understood ailments like perimenopause (Harper et al., 2022), endometriosis, and autoimmune disorders, potentially delaying diagnosis and treatment (Lindgren & Richardson, 2023; Sebring, 2021). Women with DOR experienced similar circumstances when seeking infertility diagnosis and treatment. Despite recommendations to seek reproductive care for infertility after one year of unprotected intercourse (American College of Obstetricians and Gynecologists’ Committee on Gynecologic Practice & ASRM, 2019), obstetricians and reproductive specialists dismissed patient concerns and uttered biased
opinions of “You’re young. Just keep trying,” or “You’ve been Googling too much.” For women with DOR who feel like they are ‘running out of time,’ every moment is critical to preserve what is left of their reproductive potential. Deferring infertility treatments could negatively impact ovarian reserve, leading to the need for more aggressive treatments, like IVF, and more treatment cycles to achieve pregnancy (Rasool & Shah, 2017). Overall, providers require more education about recommended practices for infertility workups and potential DOR prognoses.

While some patients may require donor eggs, it should not be discussed flippantly or as a first-line treatment in most cases. Providers are urged to consider more goal-concordant care by examining their motives behind suggesting donor eggs, increasing communication with their patients, and tailoring care to meet patient needs and desires (Elk & Gazaway, 2021; Sanders et al., 2018). An inconsiderate or hasty push for donor eggs creates the perception that providers lack experience or simply do not care to diverge from typical treatment protocols or personalize them for the individual. While it may seem like routine care to providers, it is often a complicated decision requiring lengthy conversations integrating ethical, moral, and personal values.

Similar to previous studies suggesting discrepancies between the known impact of infertility on mental health and what mental health resources are provided (Hoff et al., 2018; Salakos et al., 2004), participants in this study encountered significant emotional distress, yet providers rarely addressed mental health. Participants suggested integrating mental health screenings, infertility-specific counseling, and resources, like education, support groups, or peer-to-peer support into fertility clinics as a standard of care. Previously, peer-to-peer support programs for individuals with cancer have demonstrated
effectiveness in reducing psychological distress and improving self-efficacy and knowledge (Keimen et al., 2023), yet their efficacy in infertility care remains unknown. Additional evidence suggests that integrating mindfulness-based interventions is an effective and feasible way to reduce emotional distress, and improve quality of life in women with infertility (Wang et al., 2023). See Table 5 for a list of infertility and mental health resources.

**Clinical Implications**

This study revealed a critical need to restructure increasingly complex infertility care to improve patient satisfaction, empower patients with education, minimize mental health consequences, and progress towards goal-concordant and holistic care. Infertility-related stress can cause emotional distress, anxiety, depression, and reduced fertility quality of life (Woods et al., 2022). Women with DOR echoed these experiences and perceived several aspects of infertility care as inadequate. Fundamental changes include offering mental health screenings and resources, furnishing patients with adequate education about their diagnosis from a trusted source, like providers, ensuring transparency in care, and setting realistic expectations. Equipping patients with sufficient knowledge ensures they are treated as autonomous and active agents in their care, reducing the potential for distress from unexpected scenarios.

These findings provide a foundation for resource and intervention development and implementation for young women with DOR who are at an increased risk for psychological distress. Future research should include ethnically and racially diverse populations of women with DOR to determine possible cultural implications of infertility.
and mental health care. Potential differences in mental health between women with reproductive successes versus those who are unsuccessful and remain childless long term should also be investigated. Reproductive outcomes and mental health experiences of women with DOR who choose not to pursue treatment versus those who do would also increase understanding about DOR prognoses and the toll of infertility treatments on mental health. Awareness of the multifaceted mental health needs and perceptions of infertility care is critical in establishing a groundwork of knowledge about young women with DOR and future research and interventions to improve infertility-related mental health outcomes.

**Limitations**

Consistent with a phenomenological approach, a small sample size was used to investigate the lived experiences of young women with DOR. Participants volunteered based on eligibility criteria in the study flyer, introducing the potential for self-selection biases. It is possible that participants experienced more emotional distress than those who chose not to participate and therefore were more open to discussing their difficulties (Polit & Beck, 2021). Caution should be taken when generalizing results, as findings may not encompass all experiences with DOR, mental health, and mental health care. Infertility disproportionally affects minorities (Craig et al., 2019), yet we faced difficulties recruiting a heterogenous sample. Despite recruitment efforts, most participants represented similar racial/ethnic backgrounds and educational attainment, with only one woman identifying as multiracial. Women of racial/ethnic minorities often face socioeconomic disadvantages, an absence of insurance coverage for infertility, or
personal, religious, or social stigmas about infertility that may prevent them from seeking infertility care (Weigel et al., 2020). Because most women in this study were diagnosed with DOR after seeking infertility treatment, there may be a population of minority women with DOR who remain undiagnosed. Future studies should increase efforts to recruit racially and ethnically diverse women with DOR. Additional limitations include high educational attainment of the participants, which is linked to lifetime earnings and equitable access to health insurance, meaning individuals with a high school degree or less generally earn less and face significant health disparities accessing insurance coverage (McMorrow et al., 2019; Tamborini et al., 2015). Although all participants had postsecondary degrees, the majority lacked insurance coverage for infertility and shouldered the burden of high out-of-pocket costs for infertility treatment.

**Conclusion**

This study provided a critical patient-centered perspective on the mental health implications of DOR previously unexplored. The early diagnosis of DOR is devastating and filled with emotions of isolation, anxiety, depression, and stigma. Findings suggest fundamental changes to infertility medical and mental health care are needed, including mental health resources as a standard of care, furnishing patients with adequate education about their diagnosis from a trusted source, and ensuring transparency in care and outcome expectations. Arming patients with knowledge ensures they are autonomous and active participants in their care and reduces their risk for distress from unexpected scenarios.
| Table 5  
**Infertility-Specific Resources for Health Care Providers and Patients** |
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<td><strong>Health Care Provider Resources</strong></td>
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<td><strong>American Society for Reproductive Medicine</strong></td>
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<tr>
<td>ASRM Academy Courses and Webinars</td>
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<tr>
<td>Educational Infographics for patients and staff</td>
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<tr>
<td>Educational videos for patients and staff</td>
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<tr>
<td><strong>Patient Resources</strong></td>
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<td><strong>American Society for Reproductive Medicine</strong></td>
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<td>Reproductive Facts &amp; Education</td>
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<tr>
<td>Infertility Mental Health Professional Locations</td>
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<td><strong>Society for Assisted Reproductive Technology</strong></td>
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<td>Assisted Reproductive Technology Patient Information</td>
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<td>Patient Education Videos</td>
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<td><strong>Fertility IQ</strong></td>
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<td>Doctor &amp; Clinic Locations with Reviews</td>
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<td>Fertility &amp; Reproduction Educational Courses</td>
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<td><strong>RESOLVE: The National Infertility Association</strong></td>
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<td>RESOLVE: Support Groups, Professionals, &amp; Resources</td>
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<td>Fertility Treatment Scholarships &amp; Grants</td>
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*Note:* This is not an exhaustive list of resources.
References


Colaizzi, P. F. (1978). Psychological research as the phenomenologist views it. In R. S. Valle & M. King (Eds.), *Existential-phenomenological alternatives for psychology* (pp. 6). Oxford University Press.


CHAPTER 5

CONCLUSIONS

The purpose of this dissertation was to advance the knowledge about mental health challenges experienced by young women with DOR. This was accomplished through the development of three manuscripts. The first manuscript examined the concept of infertility-related stress and its impact on individuals with infertility. The second manuscript described the strengths and limitations of the Fertility Quality of Life tool and its utility in infertility health care. The third manuscript explored the mental health challenges and infertility health care experiences of young women with DOR. Together, the concept analysis of infertility-related stress, the quantitative results describing the FertiQoL instrument and its use in infertility care, and the qualitative findings of the mental health experiences of young women with DOR resulted in a more thorough understanding of the mental health challenges of young women with DOR and how their infertility health care can be improved. The purpose of chapter five is to present a brief summary and integration of each manuscript, discuss how these findings advance nursing research, describe the implications for future research, and present the strengths and limitations of this dissertation research.

Manuscript one examined the concept and consequences of infertility-related stress on individuals with infertility. Due to cultural differences in the personal value and beliefs surrounding infertility, articles were limited to those originating in the U.S.
Twenty-one articles were included in the review. This analysis provided crucial insight into the impact of infertility-related stress on individuals and couples with infertility. The analysis defined the antecedents, attributes, and consequences of infertility-related stress. Infertility, involuntary childlessness, and fear of the unknown were found to be antecedents of infertility-related stress. Attributes of infertility-related stress include a loss of identity, relational stress, social isolation, stigma, anxiety, depression, and a negative impact on self-esteem. Consequences include a decreased quality of life, premature discontinuation of infertility treatment, reduced relational satisfaction, increased anxiety, depression, and reduced self-esteem. This analysis resulted in a proposed definition of infertility-related stress as overwhelming mental, emotional, or physical stress resulting from the desire but inability to conceive children or from infertility treatments. By clarifying the definition of infertility-related stress, we can enhance health care providers’ ability to recognize and mitigate infertility-related stress symptoms and potentially improve infertility care and fertility-related quality of life.

Manuscript two analyzed and synthesized the reported psychometric properties of the Fertility Quality of Life instrument (FertiQoL) and described its implications for use in practice and research. This systematic review included 51 articles with no date or location restrictions. Findings revealed that the FertiQoL is a sound measurement with satisfactory face, content, convergent, and structural validity. It also indicated satisfactory reliability with adequate internal consistency, with limited evidence of relative stability over time using test-retest reliability. Additionally, some research suggested clinically significant cutoff scores that may correspond to anxiety and depression. Further corroboration of these clinically significant cutoff scores would improve provider ability
to identify individuals needing additional care. The FertiQoL can be used to differentiate the impact of infertility versus general stressors while providing a more precise determination of problem areas, like relational and emotional concerns. Although the FertiQoL can be an indispensable tool for health care providers and researchers, it still fails to depict the small nuances of why infertility affects certain areas of an individual’s life more than others. These experiences can only be captured using qualitative means.

Using a phenomenological approach, the third manuscript explored the mental health and infertility mental health care experiences of young women diagnosed with DOR. An infertility-specific adaptation of the theory of stress and coping was used to guide the qualitative data collection and describe the different perceptions of lived experiences of mental health and perceptions of mental health care during infertility. Young women with DOR reported experiencing hopelessness, anxiety, depression, loneliness, and social stigmatization during infertility. Many women expressed dissatisfaction with the lack of transparency and education provided about their diagnosis, as well as the absence of mental health care resources after receiving a devastating diagnosis. There was a universal plea for more holistic care as part of the infertility health care experience. From being transparent about treatment expectations to acknowledging the difficulty of the situation and providing mental health resources, participants felt that there is ample room for improvement in infertility-specific medical and mental health care. There was also a stark difference in treatment outcomes from one infertility clinic to another, with many participants urging others to research and find a provider specializing in DOR before choosing a clinic. The findings from this dissertation
study indicate an incongruence between the mental and medical health care needs of women with DOR and what is currently being provided by infertility clinics.

The findings from manuscript three are consistent with general infertility and mental health literature that reveals a disconnect between health care provider knowledge and infertility care. Although providers are aware of the potential mental health consequences of infertility and patients desire more mental health care resources (Dawadi et al., 2018; Domar et al., 2018; El Kissi et al., 2013), infertility health care providers are neither consistently screening for psychological distress (Hoff et al., 2018) nor providing such resources to infertility patients (Dawadi et al., 2018). Several studies have even suggested that mental health, specifically anxiety (Turner et al., 2013) and stress (Aimagambetova et al., 2020; Turner et al., 2013), may play a role in reproductive outcomes and reduced clinical pregnancy rates. Women with DOR are already at a higher risk for miscarriage and poor reproductive outcomes (Hu et al., 2020; Levi et al., 2001; Magendzo et al., 2006; Tal et al., 2021). Additional anxiety and stress from an unexpected diagnosis may compound this risk, placing them at a higher chance of experiencing psychological distress. Because of this potential and a need for more holistic care, women with DOR should be counseled about expectations related to their diagnosis, the difficulty that often accompanies DOR treatment protocols, and the possibility of negative emotional experiences during and beyond infertility.

**Strengths and Limitations**

Several methods of inquiry comprised this dissertation, including a concept analysis, systematic review, and qualitative phenomenological interviews. There are
several strengths and limitations associated with each of these methods. Because of different cultural perceptions of infertility, the concept analysis only included studies originating in the U.S. This criterion may have unintentionally omitted additional elements related to infertility-related stress. Similar to the literature included in the FertiQoL systematic review, most studies focused on population samples who pursue ART. This focus leaves out an already underrepresented sample of individuals who choose not to pursue treatment or may be unable to afford it. This limitation created a large gap of understanding regarding the impact of infertility and infertility-related stress on individuals and couples who do not receive infertility treatment.

Another limitation the concept analysis and systematic review shared is the inclusion of literature that utilized several self-report measurements. First, there is a lack of measurement standardization in the infertility literature, which made it difficult to compare rates of anxiety, depression, and infertility-related stress. Second, results from self-report measures may be vulnerable to bias (Polit & Beck, 2021) due to participants not wanting to indicate psychological distress for fear of providers canceling or delaying treatment. Lastly, few studies utilized longitudinal measurements because of the cyclical nature of hope and despair experienced as emotional responses to infertility cycles. Instead, the majority only provided measurements at one point in time, which may result in vastly different results, depending on what point during a cycle measurements were collected.

Qualitative studies also have several limitations that need to be considered. Qualitative methodology often necessitates that sampling criteria be driven by a conceptual requirement (Polit & Beck, 2021). In the case of phenomenology, this means
that participants must share the same lived experiences (Creswell & Poth, 2018). As such, purposive and snowball sampling techniques were used to recruit a small number of participants via infertility-specific social media. Although the participants were screened for eligibility after contacting the PI, they self-selected based on criteria outlined in the study flyer. Self-selection biases may be present in the study sample, potentially creating differences between those who responded to the recruitment flyer and chose to participate versus those who did not (Polit & Beck, 2021). There is a possibility that women in this dissertation study experienced more emotional distress than those who chose not to participate and therefore were more open to discussing their difficulties. Despite our efforts, the small sample of participants was relatively homogenous, with limited cultural and educational diversity among women, further limiting the generalizability of findings. Lastly, while instrumentation reliability is paramount in quantitative research, this can also be applied to qualitative studies. The researcher becomes the instrument for qualitative inquiries, exposing the data collection and analysis to personal biases and subjective interpretations (Merriam & Tisdell, 2016).

Despite the limitations described, this dissertation has several strengths. The analysis of infertility-related stress and review of the FertiQoL were performed systematically. The analysis of infertility-related stress followed each step of Rodgers’ method of concept analysis, resulting in a clarified and context-dynamic definition (Rodgers & Knafl, 2000). In addition, the systematic review was expansive, including multiple databases and all studies that have used the FertiQoL and reported psychometric properties since its creation.
The qualitative interviews were performed by the PI, who has considerable experience interviewing over 50 participants from previous studies and a personal experience with the explored phenomenon. With practice, the human instrument becomes more reliable and adept at encouraging participant conversations and elaboration on topics relevant to the topic of interest (Merriam & Tisdell, 2016; Polit & Beck, 2021). Participant trust was gained through the process of reflexivity and disclosure of the mutually shared experience and snowball sampling via two sources trusted by several participants (Creswell & Poth, 2019; Polit & Beck, 2021). The qualitative study also used videoconferencing to conduct face-to-face interviews with participants in remote locations, improving the ability to ascertain visual cues or body language (Polit & Beck, 2021).

Advancing Nursing Research

This dissertation contributed to advancing nursing research by generating three manuscripts that further the understanding of mental health in women with infertility and diminished ovarian reserve. This dissertation provided important information about the significance of infertility-related stress and how to recognize it, addressed the consequences of infertility on fertility quality of life, including measurements that can be used to identify areas of concern, and provided a critical patient-centered perspective on the implications of DOR on mental health that has been previously unexplored. Examining infertility-related stress contributed to the body of knowledge linking the significant impact of infertility on mental health. It describes the potential of experiencing emotional distress, anxiety, depression, and a reduced fertility quality of
life. Women with DOR echoed these experiences and identified several aspects of infertility care they perceived as inadequate. This dissertation generated evidence that supports a need for fundamental changes to infertility medical and mental health care, including offering mental health screenings and resources as a standard of care, furnishing patients with adequate education about their diagnosis from a trusted source like their provider, and ensuring transparency in care and outcome expectations. Nurse researchers can use these findings as a foundation for developing and implementing interventions and resources for young women with DOR who are at an increased risk for psychological distress. Equipping patients with sufficient knowledge ensures they are treated as autonomous agents and active participants in their care, thus reducing the potential for distress from unexpected scenarios.

**Implications for Future**

This dissertation demonstrates a critical need to restructure increasingly complex infertility care to improve patient satisfaction, empower patients with education, reduce mental health consequences, and progress towards more goal-concordant and holistic infertility care. Future research should strive to include a more ethnically and racially diverse population of women with DOR to determine possible cultural implications on the perceptions of infertility care and mental health. Moving forward, research should also aim to investigate potential differences in mental health between women with reproductive successes versus those who are unsuccessful and remain childless long term. A comparison of reproductive outcomes and mental health experiences between women with DOR who choose not to pursue treatment and those who do would also serve to
increase understanding not only about reproductive outcomes of DOR but also the toll that infertility treatments can take on mental health. Awareness of the multifaceted mental health needs and perceptions of infertility care is critical in establishing a groundwork of knowledge about young women with DOR and developing future research and interventions to improve infertility-related mental health outcomes.
References


APPENDIX A

UNIVERSITY OF ALABAMA AT BIRMINGHAM INSTITUTIONAL REVIEW BOARD APPROVAL LETTER
APPROVAL LETTER

TO: Woods, Brittany Munger

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 21-Nov-2022

RE: IRB-300010065
IRB-300010065-002
Exploring the Mental Health Lived Experiences of Young Women with Diminished Ovarian Reserve

The IRB reviewed and approved the Initial Application submitted on 04-Nov-2022 for the above referenced project. The review was conducted in accordance with UAB’s Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Exempt
Exempt Categories: 2
Determination: Exempt
Approval Date: 21-Nov-2022
Approval Period: No Continuing Review

The following apply to this project related to informed consent and/or assent:

- Waiver of HIPAA

Documents Included in Review:

- IRB EPORTFOLIO
- IRB PERSONNEL EFORM
APPENDIX B

DIMINISHED OVARIAN RESERVE AND MENTAL HEALTH RECRUITMENT FLYER
DIMINISHED OVARIAN RESERVE & MENTAL HEALTH

Contact us to participate in a research study about mental health in young women with infertility caused by diminished ovarian reserve.

TO PARTICIPATE, YOU MUST:
- Be diagnosed with infertility caused by diminished ovarian reserve by the age of 35
- Have experienced mental health challenges, like anxiety or depression, as a result of your diagnosis
- Have never been diagnosed with cancer or received chemotherapy/radiation
- Have not had any surgical procedures on your ovaries, uterus, or pelvic area before infertility
- Do not have a history of severe mental illness requiring hospitalization before infertility
- Speak English
- Have a working telephone number, email account, and internet connection

ABOUT THE STUDY:
Our goal is to learn about the mental health experiences of young women who have been diagnosed with infertility caused by diminished ovarian reserve.

IF YOU PARTICIPATE IN THIS STUDY, YOU WILL BE INVITED TO:
1) Take a short survey about yourself, your infertility, and your mental health
2) Take part in an interview lasting 60-90 minutes
3) Receive $30 compensation for your time

FOR MORE INFORMATION, CONTACT: Brittany Woods, BSN, RN brittwoods@uab.edu
Scan or click the QR Code for more information
APPENDIX C

QUALITATIVE INTERVIEW PROTOCOL
Thank you for agreeing to speak with me today. My name is [insert research team member] and I am the [insert role as Principal Investigator, Co-Investigator, or Research Assistant] of this study at the University of Alabama at Birmingham. In this study we would like to better understand the mental health experiences of young women with diminished ovarian reserve and how they perceive their mental health care. Today, we are interested in learning more about your experiences of mental health during infertility and how, if at all, your mental health was addressed by your clinicians.

I hope to have 60 to 90 minutes of your time.

This interview is confidential, and you will be identified by an identification number only. To protect your privacy, please do not use your name, or any identifying information. Answering questions is voluntary, and you may skip any question you do not choose to answer. Please feel free to add anything you would like to, or that you feel better explains your answer. There are no foreseeable risks to you associated with this project, nor are there any direct benefits. You may end this interview at any time if you should feel uncomfortable or for any reason. We can stop the interview if you need a break, and resume when you are ready.

I will be recording the interview; however, I will not share this recording with anyone besides individuals who are part of our research team at the University of Alabama at Birmingham. Do you have any questions for me before we start the interview and the recorder is turned on?

OK, let’s get started…[TURN RECORDER ON]

1) To begin, do you give your consent to participate in this interview and be recorded? [WAIT FOR CONSENT]

2) Next, I would like to hear a little bit about yourself. Tell me the following basic information:
   a. How old are you?
   b. Tell me about your infertility journey and where you are with it as of now.
   c. (If not already discussed) Have you used any fertility treatments in the past? What was the result of those?
   d. (If not already discussed) How long have you been trying to conceive?
e. *(If not already discussed)* Do you have any children or prior pregnancies? Were these pregnancies conceived naturally, with fertility treatments, adoption, or stepchildren?

**Okay great. My next few questions have to do with your experience of your diagnosis of diminished ovarian reserve.**

3) How old were you when you were diagnosed with diminished ovarian reserve?
   
   a. *What was your reaction to the diagnosis of diminished ovarian reserve?*
   
   b. *What was your understanding of diminished ovarian reserve?*
   
   c. *Can you tell me a little bit about how, if ever, it has been explained to you? If yes, How do you feel the conversation could have been improved?*

4) How do you think having this diagnosis affected your infertility journey and treatments?

**The next set of questions pertain more to the mental health aspects of your diagnosis and infertility journey.**

5) How would you describe your mental health during infertility? These could be positive or negative experiences, like having anxiety or depression or being hopeful or sad.

6) What have your fertility clinicians done to address the mental health or impact of your DOR diagnosis?
   
   a. *What resources did they provide?*

7) Were there any other clinicians that addressed your mental strain from this diagnosis, like your primary care doctor, OB/GYN, or a psychiatrist?
   
   a. *How did they address it and what resources were provided by these clinicians?*

8) What have you found helpful in coping with and managing your mental health?
   
   a. *Have you sought out any resources on your own and if so, which ones (i.e. therapy, medications, support groups)?*
   
   b. *How do you feel about your support system?*
   
   c. *Is there anything that has made it more difficult to cope with your diagnosis or that you have found to be unhelpful?*

9) How do you think your medical team could better meet the mental health needs of patients similar to you when facing this diagnosis?
10) What resources would you like to see provided as part of a counseling session with your clinicians regarding your diagnosis and mental health that would help you the most?

11) Is there anything that I didn’t ask that you were surprised about or is there anything else that you feel like needs to be talked about?

12) What final thoughts and advice do you have for us regarding the needs and challenges of young women with DOR related to mental health?

Thank you so much for your time. I am going to stop the recording now.
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